PATENT
Attorney Docket No.: 01289.0002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE #23

In re: U.S. Patent 4,746,680

Issued: May 24, 1988

To: James E. Jeffery, Antonin Kozlik, and Eric C. Wilmshurst

Assignee: Knoll AG

Title of Patent: THERAPEUTIC AGENTS

Assistant Commissioner for Patents
Box Patent EXT.
Washington, D.C. 20231

HAND DELIVERY
OFFICE OF PETITIONS
Crystal Park 1-520

Sir:

APPLICATION FOR PATENT TERM EXTENSION UNDER 35 U.S.C. § 156

Transmitted herewith is an application for patent term extension of U.S. Patent No. 4,746,680. The application is submitted as one original and four (4) copies.

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Respectfully submitted,

Charles E. Van Horn

Charles E. Van Horn
Reg. No. 40,266

Dated: January 20, 1998

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	U.S. Patent 4,746,680
Issued:	May 24, 1988
To:	James E. Jeffery, Antonin Kozlik, and Eric C. Wilmshurst
Assignee:	Knoll AG
Title of Patent:	THERAPEUTIC AGENTS

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Your applicant, Knoll Aktiengesellschaft, represents that it is the owner of record of the entire interest in and to Letters Patent of the United States No. 4,746,680 granted to James E. Jeffery, Antonin Kozlik, and Eric C. Wilmshurst on the 24th day of May, 1988 for THERAPEUTIC AGENTS. Knoll AG is the owner of record by virtue of an assignment in favor of Knoll AG recorded November 7, 1995, Reel 7696, Frame 0572. By the Power of Attorney enclosed herein (Attachment A), Applicant appoints Charles E. Van Horn, Esq. of Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P., as attorney for Knoll Aktiengesellschaft with

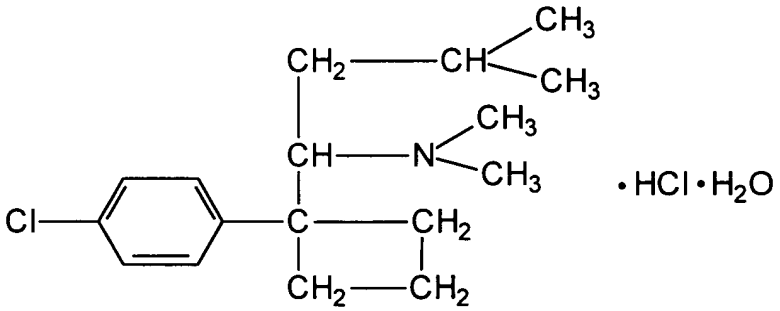
regard to this application for extension of the term of U.S. Patent No. 4,746,680 and to transact all business in the U.S. Patent and Trademark Office in connection therewith.

Applicant hereby submits this application for extension of patent term under 35 U.S.C. § 156 by providing the following information required by the rules promulgated by the U.S. Patent and Trademark Office (37 C.F.R. § 1.740). For the convenience of the Patent and Trademark Office, the information contained in this application will be presented in a format which will follow the requirements of 37 C.F.R. § 1.740.

1. "A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics." 37 C.F.R § 1.740 (a)(1).

The approved product is MERIDIA® (sibutramine hydrochloride monohydrate) Capsules. The generic name for the approved product is sibutramine hydrochloride monohydrate, which is indicated for the long-term management of obesity, including weight loss and maintenance of weight loss.

(a) Structural Formula:



(b) Empirical Formula:

$C_{17}H_{29}Cl_2NO$

(c) Molecular Weight

334.33

(d) Chemical names:

1. Cyclobutanemethanamine, 1-(4-chlorophenyl)-*N,N*-dimethyl-α-(2-methylpropyl)-, hydrochloride, monohydrate, (±)

2. (±)-1-(p-Chlorophenyl)-α-isobutyl-*N,N*-dimethylcyclobutanemethylamine hydrochloride monohydrate

3. N-{1-[1-(4-Chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N-dimethylamine hydrochloride monohydrate

2. "A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred." 37 C.F.R § 1.740 (a)(2).

Section 505 of the Federal Food, Drug, and Cosmetic Act (FDC Act), 21 U.S.C. § 355, is the Federal statute under which the Food and Drug Administration's (FDA's) regulatory review of Knoll Pharmaceutical Company's MERIDIA® new drug application (NDA) for sibutramine hydrochloride monohydrate occurred. Section 505(b) of the FDC Act, 21 U.S.C. § 355 (b), authorizes the filing of an NDA for a "new drug." FDA subsequently approved the MERIDIA®

NDA (NDA 20-632) under the authority granted the agency in Section 505(c) of the FDC Act, 21 U.S.C. & 355(c).

3. **"An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred." 37 C.F.R. § 1.740 (a)(3).**

On November 22, 1997, the FDA approved Knoll Pharmaceutical Company's MERIDIA® (sibutramine hydrochloride monohydrate) NDA under Section 505 of the FDC Act. Approval of the NDA authorizes the first commercial marketing of sibutramine hydrochloride monohydrate.

4. **"In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act." 37 C.F.R. § 1.740 (a)(4).**

The active ingredient in MERIDIA® is sibutramine hydrochloride monohydrate which has not been previously approved for commercial marketing or use under the FDC Act, the Public Health Service Act, or the Virus-Serum-Toxin Act prior to the approval of the MERIDIA® NDA on November 22, 1997.

5. **"A statement that the application is being submitted within the sixty day period permitted for submission pursuant to 37 C.F.R. 1.720 (f) and an identification of the date of the last day on which the application could be submitted." 37 C.F.R. § 1.740 (a)(5).**

This application is being submitted within the sixty day period following FDA approval of the MERIDIA® NDA. FDA approved the MERIDIA® on November 22, 1997. The sixty day period for submission of this patent extension application will expire on January 21, 1997.

6. **"A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration." 37 C.F.R. § 1.740 (a)(6).**

Knoll Aktiengesellschaft is seeking an extension of U.S. Patent No. 4,746,680. The inventors are James E. Jeffery, Antonin Kozlik, and Eric C. Wilmshurst. The date of issue for the patent is May 24, 1988, and the date of expiration is June 11, 2002.

7. **"A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings." 37 C.F.R. § 1.740 (a)(7).**

A copy of the patent for which an extension is being sought is attached to this application (Attachment B). The patent contains thirty-four claims and no drawings.

8. **"A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent." 37 C.F.R. § 1.740 (a)(8).**

There is no certificate of correction or reexamination certificate issued for U.S. Patent No. 4,746,680. A copy of the terminal disclaimer issued for U.S. Patent No. 4,746,680 is attached (Attachment C). The patent application for U.S. Patent No. 4,746,680 was filed on April 19, 1985, and a patent was issued on May 24, 1988. Under 35 U.S.C. § 41(b)(1), a maintenance fee was due in the United States Patent and Trademark Office on November 29, 1991. The maintenance fee was paid on September 30, 1991. Under 35 U.S.C. § 41(b)(2), a second maintenance fee was due in the United States Patent and Trademark Office on November

29, 1995. The maintenance fee was paid on September 26. 1995. A copy of the printout of the Maintenance Status showing the payments is attached (Attachment D).

9. **"A statement that the patent claims the approved product or a method of using . . . the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which each applicable patent claim reads on the approved product or a method of using . . . the approved product." 37 C.F.R. § 1.740 (a)(9).**

U.S. Patent No. 4,746,680 claims the approved product, sibutramine hydrochloride monohydrate, a pharmaceutical composition containing the approved product, and a method of using the approved product. Sibutramine hydrochloride monohydrate is a pharmaceutically acceptable salt of N, N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine. The patent claims are as follows: claims 1-6, 9, 11, 14-19, 22, 24, 26-31 and 34.

These claims read on the approved product when:

R_1 is a branched alkyl containing 4 carbon atoms (or isobutyl)

R_2 is H

R_3 is an alkyl containing 1 carbon atom (or methyl)

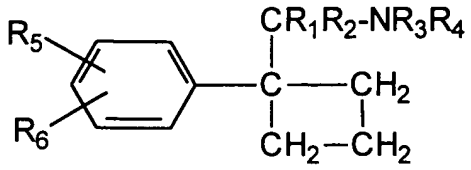
R_4 is an alkyl containing 1 carbon atom (or methyl)

R_5 is halo (Chloro)

R_6 is H

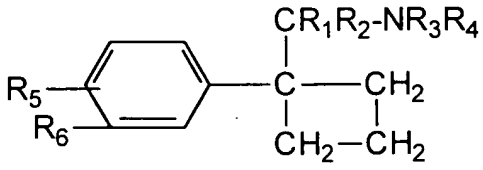
as shown in the identification of the approved product in paragraph (1.) above. Representative claims from U.S. Patent 4,746,680 are reproduced below.

1. A compound of the formula I:



or a pharmaceutically acceptable salt thereof in which R_1 is branched chain alkyl of up to 6 carbon atoms, in which R_2 is selected from the group consisting of H and alkyl groups containing 1 to 3 carbon atoms; in which R_3 and R_4, which are the same or different, are selected from the group consisting of H, straight or branched chain alkyl groups containing 1 to 4 carbon atoms, alkenyl groups having 3 to 6 carbon atoms, alkynyl groups having 3 to 6 carbon atoms, cycloalkyl groups in which the ring contains 3 to 7 carbon atoms, and a group of formula CHO; in which R_5 and R_6, which are the same or different, are selected from the group consisting of H, halo, trifluoromethyl, alkyl groups containing 1 to 3 carbon atoms, alkoxy groups containint from 1 to 3 carbon atoms, alkythio groups containing 1 to 3 arbon atoms and phenyl, or R_5 and R_6, together with the carbon atoms to which they are attached, form a second benzene ring optionally substituted by at least one halo, alkyl or alkoxy group containing 1 to 4 carbon atoms or the substituents of the second benzene ring together with the two carbon atoms to which they are attached form a further benzene ring.

9. A compound according to claim 1 of the formula III:



or a pharmaceutically acceptable salt thereof in which R_1 is isobutyl; R_2 is H; R_3 is H, methyl, or ethyl; R_4 is H, methyl, or ethyl; R_5 is chloro; and R_6 is H or chloro.

11. A compound of claim 9 which is N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine or a pharmaceutically acceptable salt thereof.

The FDA approved labeling for sibutramine hydrochloride monohydrate capsules - which will be marketed under the trade name MERIDIA® - states that the drug is sibutramine hydrochloride monohydrate

In terms of dosage, the FDA approved labeling states that the usual dosage is 10 milligrams once a day with a maximum dose of 15 milligrams a day, with the reservation that a dose of 5 milligrams a day may be administered to those patients who cannot tolerate a dose of 10 milligrams a day.

10. **"A statement . . . of the relevant dates and information pursuant to 35 U.S.C. § 156(g) in order to enable the Secretary of Health and Human Services . . . to determine the applicable regulatory review period . . . For a patent claiming a human drug . . ., the effective date of the investigational new drug (IND) application and the IND number; the date on which a new drug application (NDA) . . . was initially submitted . . . and the date on which the NDA was approved . . . " 37 C.F.R. § 1.740 (a)(10), (I).**

In order to enable the Secretary to determine the applicable regulatory review period, the following information is provided.

(a) Knoll Pharmaceutical Company (formerly Boots Pharmaceuticals, Inc.) filed its IND application for sibutramine hydrochloride monohydrate (IND 27-624) on December 20, 1985 and it became effective on January 24, 1986.

(b) Knoll Pharmaceutical Company's MERIDIA® NDA (NDA 20-632) was initially submitted to the FDA on August 7, 1995.

(c) The MERIDIA® NDA (NDA 20-632) was approved by the FDA on November 22, 1997.

11. **"A brief description . . . of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant date applicable to such activities." 37 C.F.R. § 1.740 (a)(11).**

Attached is a chronology that briefly describes the significant regulatory activities and relevant dates associated with Knoll Pharmaceutical Company's prosecution of this product before the FDA (Attachment E).

12. "A statement . . .that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined." 37 C.F.R. § 1.740 (a)(12).

(i) It is the opinion of the applicant that U.S. Patent No. 4,746,680 is eligible for an extension. This opinion is based on the following information on U.S. Patent No. 4,746,680:

(a) 35 U.S.C. § 156 (a) - U.S. Patent No. 4,746,680 claims the approved human drug product sibutramine hydrochloride monohydrate, MERIDIA®.

(b) 35 U.S.C. § 156 (a) (1) - The term of the patent has not expired prior to the submission of this application.

(c) 35 U.S.C. § 156(a) (2) - The term of said patent has never been previously extended under 35 U.S.C. § 156 (e) (1).

(d) This application for extension is in compliance with 37 C.F.R. § 1.740.

(e) 35 U.S.C. § 156 (a) (4) - The product, MERIDIA®, has been subject to a regulatory review period as defined in 35 U.S.C. § 156 (g) before its commercial marketing or use.

(f) 35 U.S.C. § 156 (a) (5) (A) - The product received permission for commercial marketing or use on November 22, 1997 and this is the first permitted commercial marketing or use under the provision of law (i.e., FDC Act § 505) under which the applicable regulatory review occurred.

(g) The application has been submitted within sixty days from the November 22, 1997 approval date.

(h) 35 U.S.C. § 156 (c) (4) - No other patent term has been extended for the same regulatory review period for this product.

(ii) It is the opinion of the applicant that U.S. Patent No. 4,746,680 is eligible for an extension of 1,825 days from June 11, 2002 to June 11, 2007. The length of this extension was determined as follows:

(A) The effective date of the IND application is January 24, 1986 and the IND number is 27-624.

(B) The NDA, No. 20-632, was initially submitted to the FDA on August 7, 1995.

(C) The NDA was approved by the FDA on November 22, 1997.

(D) U.S. Patent No. 4,746,680 was issued on May 24, 1988.

The following calculation of the regulatory review period is in accordance with 37 C.F.R. 1.775:

A to B = 3493 days	(37 C.F.R. § 1.775 (c)(1))
B to C = 828 days	(37 C.F.R. § 1.775 (c)(2))
A to D = 852 days	(37 C.F.R. § 1.775 (d)(1)(i))

4,321 - 852 = 3,469 days (37 C.F.R. § 1.775 (d)(1)(i))

3,469 - 1/2(3,469-828) = 2,148.5 days (37 C.F.R. § 1.775 (d)(1)(ii))

(a) Section 1.775 (d) (4) requires the earlier date of either §§ 1.775 (d) (2) and (d) (3):

(d) (2) = June 11, 2002 + 2,148 days = May 9, 2008

(d) (3) = November 22, 1997 + 14 years = November 22, 2011

(b) Section 1.775 (d) (6) (ii) (B) further requires the earlier date of either (d) (4) or (d) (6) (I) (A):

(d) (4) = May 9, 2008

(d) (6) (I) (A) = June 11, 2002 + 5 years = June 11, 2007

This extends the patent through June 11, 2007, which is the longest period allowed under Section 1.775 (d).

13. "A statement that the applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services . . . any information which is material to the determination of entitlement to the extension sought." 37 C.F.R. 1.740 (a)(13).

The applicant hereby acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

14. **"The prescribed fee for receiving and acting upon the application for extension." 37 C.F.R. § 1.740 (a)(14).**

In accordance with the fee schedule set out in 37 C.F.R. § 1.20 (j) (1), enclosed is a check in the amount of **$1,120.00.** The Commissioner is authorized to charge any additional fees required by this application to Deposit Account No. 09-0425.

15. **"The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for the patent term extension are to be directed." 37 C.F.R. § 1.740 (a)(15).**

Please direct all inquiries and correspondence relating to this application for patent term extension to:

Charles E. Van Horn, Esq.
Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.
1300 I Street, N.W.
Washington, D.C. 20005-3315

Tel: (202) 408-4000
Fax: (202) 408-4400

16. **"A duplicate of the application papers certified as such." 37 C.F.R. § 1.740 (a)(16).**

Enclosed is a certification that this application for patent extension, including its attachments, is being submitted as one original and four (4) copies thereof (Attachment F).

17. **"An oath or declaration [submitted in compliance with] paragraph (b) of this section." 37 C.F.R. § 1.740 (a)(17).**

The requisite declaration pursuant to 37 C.F.R. § 1.740 (b) is attached (Attachment G).

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

By: Charles E. Van Horn

Charles E. Van Horn
Reg. No. 40,226

Dated:

Attachments:

Power of Attorney (Attachment A)
U.S. Patent 4,746,680 (Attachment B)
Terminal Disclaimer (Attachment C)
Copy of Maintenance Fee Payments (Attachment D)
Chronology of Significant Activities (Attachment E)
Certification of Copies of Application Papers (Attachment F)
Declaration Pursuant to 37 C.F.R. § 1.740(b) (Attachment G)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	U.S. Patent 4,746,680
Issued:	24 May, 1988
To:	James E. Jeffery, Antonin Kozlik, and Eric C. Wilmshurst
Assignee:	Knoll AG
Title of Patent:	THERAPEUTIC AGENTS

POWER OF ATTORNEY

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Knoll Aktiengesellschaft (Knoll AG) is the owner of record of the entire interest in and to Letters Patent of the United States No. 4,746,680 granted to James E. Jeffery, Antonin Kozlik, and Eric C. Wilmshurst on the 24th day of May, 1988 for THERAPEUTIC AGENTS.

Knoll AG is the owner of record by virtue of an assignment in favor of Knoll AG recorded November 7, 1995, Reel 7696, Frame 0572.

Knoll AG hereby appoints the following

1. Charles E. Van Horn, Esq.
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as its attorneys and agent to transact all business with the United States Patent and Trademark Office in connection with its Application for Extension of Patent Term under 35 USC §156 for US Patent 4,746,680.

Respectfully submitted,

Knoll Aktiengesellschaft

ppa. Kahlstorff ppa. Dr. Biesalski

Date: _____

United States Patent [19]

Jeffery et al.

[11] **Patent Number: 4,746,680**

[45] **Date of Patent: * May 24, 1988**

[54] **THERAPEUTIC AGENTS**

[75] Inventors: **James E. Jeffery; Antonin Kozlik; Eric C. Wilmshurst, all of Nottingham, United Kingdom**

[73] Assignee: **The Boots Company p.l.c., England**

[*] Notice: The portion of the term of this patent subsequent to Jun. 11, 2002 has been disclaimed.

[21] Appl. No.: **725,206**

[22] Filed: **Apr. 19, 1985**

Related U.S. Application Data

[63] Continuation of Ser. No. 365,285, Apr. 5, 1982, Pat. No. 4,522,328.

[30] **Foreign Application Priority Data**

Apr. 6, 1981 [GB] United Kingdom 8110709

[51] **Int. Cl.**[4] **A01N 33/02**

[52] **U.S. Cl.** **514/646**; 564/305; 544/403; 546/346; 546/348; 548/578; 514/242; 514/277; 514/359; 514/408

[58] **Field of Search** 564/305; 544/403; 546/346, 348; 548/578; 514/646, 247, 277, 359, 408

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,443,449	4/1984	Jeffery et al.	514/646 X
4,522,828	6/1985	Jeffery et al.	514/247 X

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Chem. Abs., 85, 32678y—Aminoesters of 1-(Alpha-Naphthyl) Cycloalkane-1-Carboxylic Acids and 1-(Alpha-Naphthyl) Cycloalkane-1-Methyl Guanidines in Russian and copy of English translation attached.

Arya and Shenoy—Synthesis of New Heterocycles, Indian Journal of Chemistry, 14B, 766-769 (1976).

Armyanskii Khimichesdii Zhurnal, 29, No. 2, 194-199 (1976).

"Neurotransmitters and Drugs", by Kruk and Pycock, Croom Helm London, p. 149.

Nieforth and Cohen, "Central Nervous System Stimulants", Chapter 13 of the book entitled Principles of Medicinal Chemistry, by Foye, second edition, Lea & Febiger, 1981, Phil., pp. 303-316.

Israel Journal of Chemistry 13 No. 2 (1975), pp. 125-136, A. Kalir, "1-Phenylcycloalkylamine Derivatives III".

"1-Phenylcycloalkylamine Derivatives. II, Synthesis and Pharmacological Activity", A. Kalir, (1969), pp. 473-477, of vol. 12, J. Med. Chem.

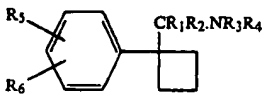
Kalir, et al., 1-Phenylcycloakylamine Derivatives I, Israel Journal of Chemistry 5 (1967), pp. 223-229.

Primary Examiner—Paul F. Shaver

Attorney, Agent, or Firm—Jacobs & Jacobs

[57] **ABSTRACT**

Compounds of formula I



in which R_1 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, cycloalkylalkyl or optionally substituted phenyl; R_2 is H or C_{1-3} alkyl; R_3 and/or R_4 are H, formyl, C_{1-3} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, C_{3-7} cycloalkyl or R_3 and R_4 together with the nitrogen atom form a heterocyclic ring system; R_5 and/or R_6 are H, halo, CF_3, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylthio or R_5 and R_6 together with the carbon atoms to which they are attached form a second benzene ring show therapeutic activity in the treatment of depression. Pharmaceutical compositions and processes for preparing compounds of formula I are disclosed.

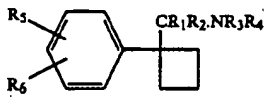
34 Claims, No Drawings

THERAPEUTIC AGENTS

This is a continuation of application Ser. No. 365,285, filed Apr. 5, 1982, now U.S. Pat. No. 4,522,328.

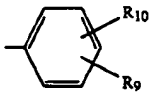
This invention relates to compounds having useful therapeutic activity as antidepressants, to pharmaceutical compositions containing such compounds and to processes for the preparation of such compounds.

The present invention provides compounds of formula I



I

in which R_1 is a straight or branched chain alkyl group containing 1 to 6 carbon atoms, a cycloalkyl group containing 3 to 7 carbon atoms, a cycloalkylalkyl group in which the cycloalkyl group contains 3 to 6 carbon atoms and the alkyl group contains 1 to 3 carbon atoms, an alkenyl group or an alkynyl group containing 2 to 6 carbon atoms or a group of formula II



II

in which R_9 and R_{10}, which may be the same or different, are H, halo or an alkoxy group containing 1 to 3 carbon atoms;

in which R_2 is H or an alkyl group containing 1 to 3 carbon atoms;

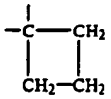
in which R_3 and R_4, which may be the same or different, are H, a straight or branched chain alkyl group containing 1 to 4 carbon atoms, an alkenyl group having 3 to 6 carbon atoms, an alkynyl group having 3 to 6 carbon atoms, a cycloalkyl group in which the ring contains 3 to 7 carbon atoms, a group of formula $R_{11}CO$ where R_{11} is H or R_3 and R_4 together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic ring having 5 or 6 atoms in the ring which may contain further hetero atoms in addition to the nitrogen atom;

in which R_5 and R_6, which may be the same or different, are H, halo, trifluoromethyl, an alkyl group containing 1 to 3 carbon atoms, an alkoxy or alkylthio group containing 1 to 3 carbon atoms, phenyl or R_5 and R_6, together with the carbon atoms to which they are attached, form a second benzene ring which may be substituted by one or more halo groups, an alkyl or alkoxy group containing 1 to 4 carbon atoms or the substituents of the second benzene ring together with the two carbon atoms to which they are attached may form a further benzene ring;

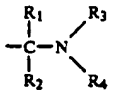
and their pharmaceutically acceptable salts.

In the formulae included in this specification the symbol

represents a 1,1-disubstituted cyclobutane group of formula



and $—CR_1R_2.NR_3R_4$ represents a group of formula

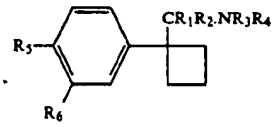


In the preferred compounds of formula I R_1 is a straight or branched chain alkyl group containing 1 to 4 carbon atoms, a cycloalkyl group containing 3 to 7 carbon atoms, a cycloalkylmethyl group in which the cycloalkyl ring contains 3 to 6 carbon atoms or a group of formula II in which R_9 and/or R_{10} are H, fluoro or methoxy and in which R_2 is H or methyl. Examples of particularly preferred compounds of formula I are those in which R_2 is H and R_1 is methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl or phenyl.

In preferred compounds of formula I, R_3 and/or R_4 are hydrogen, methyl, ethyl or formyl or R_3 and R_4 together with the nitrogen atom to which they are attached form a heterocyclic ring containing one nitrogen atom and 4 or 5 carbon atoms which is optionally substituted by one or more alkyl groups or R_3 and R_4 together with the nitrogen atom to which they are attached form a heterocyclic ring containing a second nitrogen atom which is optionally alkylated or a heterocyclic ring including one or more double bonds.

In preferred compounds of formula I R_5 and/or R_6 are H, fluoro, chloro, bromo, iodo, trifluoromethyl, methyl, methoxy, phenyl or R_5 and R_6 together with the carbon atoms to which they are attached form a second benzene ring which may optionally be substituted by halo.

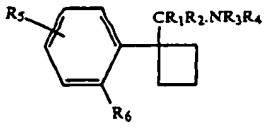
A first group of preferred compounds of formula I is represented by formula III



III

in which R_5 and R_6 are as defined above. In preferred compounds of formula III R_5 and R_6, which may be the same or different, are H, fluoro, chloro, bromo, iodo, trifluoromethyl, methyl, methoxy, phenyl or in which R_5 and R_6 together with the carbon atoms to which they are attached form a second benzene ring which may optionally be substituted by a chloro group. In particularly preferred compounds of formula III R_5 and/or R_6 are H, fluoro, chloro, iodo, trifluoromethyl, methyl, phenyl or R_5 and R_6 together with the carbon atoms to which they are attached form a second benzene ring which may optionally be substituted by a chloro group.

A second group of preferred compounds of formula I is represented by formula IV



IV

in which R_5 may be H, fluoro, chloro, bromo, iodo, trifluoromethyl, methyl, methoxy or phenyl and in which R_6 is fluoro or methyl. In particular preferred compounds of formula IV R_5 is H or chloro.

Compounds of formula I may exist as salts with pharmaceutically acceptable acids. Examples of such salts include hydrochlorides, maleates, acetates, citrates, fumarates, tartrates, succinates and salts with acidic amino acids such as aspartic and glutamic acids.

Compounds of formula I which contain one or more asymmetric carbon atoms can exist in different optically active forms. When R_1 and R_2 are different or R_7 and R_8 are different, the compounds of formula I contain a chiral centre. Such compounds exist in two enantiomeric forms and the present invention includes both enantiomeric forms and mixtures thereof. When R_1 and R_2 are different and R_1 contains a chiral centre the compounds of formula I contain two chiral centres and the compounds exist in four diastereoisomeric forms. The present invention includes each of these diastereoisomeric forms and mixtures thereof.

The present invention also includes pharmaceutical compositions containing a therapeutically effective amount of a compound of formula I together with a pharmaceutically acceptable diluent or carrier.

In therapeutic use, the active compound may be administered orally, rectally, parenterally or topically, preferably orally. Thus the therapeutic compositions of the present invention may take the form of any of the known pharmaceutical compositions for oral, rectal, parenteral or topical administration. Pharmaceutically acceptable carriers suitable for use in such compositions are well known in the art of pharmacy. The compositions of the invention may contain 0.1–90% by weight of active compound. The compositions of the invention are generally prepared in unit dosage form.

Compositions for oral administration are the preferred compositions of the invention and these are the known pharmaceutical forms for such administration, for example tablets, capsules, syrups and aqueous or oily suspensions. The excipients used in the preparation of these compounds are the excipients known in the pharmacists' art. Tablets may be prepared by mixing the active compound with an inert diluent such as calcium phosphate in the presence of disintegrating agents, for example maize starch, and lubricating agents, for example magnesium stearate, and tableting the mixture by known methods. The tablets may be formulated in a manner known to those skilled in the art so as to give a sustained release of the compounds of the present invention. Such tablets may, if desired, be provided with enteric coatings by known methods, for example by the use of cellulose acetate phthalate. Similarly, capsules, for example hard or soft gelatin capsules, containing the active compound with or without added excipients, may be prepared by conventional means and, if desired, provided with enteric coatings in a known manner. The tablets and capsules may conveniently each contain 1 to 500 mg of the active compound. Other compositions for oral administration include, for example, aqueous suspensions containing the active compound in an aqueous medium in the presence of a non-toxic suspending agent such as sodium carboxymethylcellulose, and oily suspensions containing a compound of the present invention in a suitable vegetable oil, for example arachis oil.

Compositions for the invention suitable for rectal administration are the known pharmaceutical forms for such administration, for example suppositories with cocoa butter or polyethylene glycol bases.

Compositions of the invention suitable for parenteral administration are the known pharmaceutical forms for such administration, for example sterile suspensions in aqueous and oily media or sterile solutions in a suitable solvent.

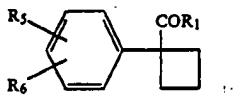
Compositions for topical administration may comprise a matrix in which the pharmacologically active compounds of the present invention are dispersed so that the compounds are held in contact with the skin in order to administer the compounds transdermally. Alternatively the active compounds may be dispersed in a pharmaceutically acceptable cream or ointment base.

In some formulations it may be beneficial to use the compounds of the present invention in the form of particles of very small size, for example as obtained by fluid energy milling.

In the compositions of the present invention the active compound may, if desired, be associated with other compatible pharmacologically active ingredients.

The pharmaceutical compositions containing a therapeutically effective amount of a compound of formula I may be used to treat depression in mammals including human beings. In such treatment the amount of the compound of formula I administered per day is in the range 1 to 1000 mg preferably 5 to 500 mg.

Compounds of formula I in which R_4 is CHO may be prepared by the reductive amidation of ketones of formula V



V

for example with formamide and formic acid or ammonium formate and formic acid to give compounds of formula I in which R_4 is CHO and R_3 is H or with formamides of formula $HCONHR_3$ in which R_3 is an alkyl or cycloalkyl group and formic acid or amines of formula R_3NH_2 in which R_3 is an alkyl or cycloalkyl group and formic acid.

Compounds of formula I in which R_4 is CHO may be prepared by the formylation of compounds of Formula I in which R_4 is H for example by reaction with methyl formate.

Compounds of formula I in which R_3 is other than H and R_4 is CHO may be prepared by reacting compounds of formula I in which R_3 is H and R_4 is CHO with a compound of formula R_3X where X is a leaving group such as a halo group in the presence of a base.

Compounds of formula I may be prepared by the reductive amination of ketones of formula V.

Examples of suitable reductive amination processes are given below:

(a) for compounds of formula I in which R_3 and R_4 are H, by reaction of the ketone with an ammonium salt

for example ammonium acetate and a reducing agent such as sodium cyanoborohydride,

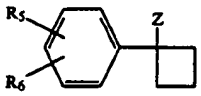
(b) for compounds of formula I in which R_3 is alkyl or cycloalkyl and R_4 is H by reaction of the ketone with an amine of formula R_3NH_2 and a reducing agent such as sodium cyanoborohydride or sodium borohydride,

(c) for compounds of formula I in which neither R_3 nor R_4 is hydrogen or in which R_3 and R_4 together with the nitrogen atom form a heterocyclic ring, by reaction of the ketone with an amine of formula HNR_3R_4 and either formic acid or a reducing agent such as sodium cyanoborohydride,

(d) for compounds of formula I in which one or both of R_3 and R_4 are H or an alkyl or a cycloalkyl group or in which R_3 and R_4 together with the nitrogen atom form a heterocyclic ring, by catalytic hydrogenation at elevated temperature and pressure of a mixture of the ketone and an amine of formula HNR_3R_4.

Compounds of formula I in which R_3 and R_4 are both alkyl groups may be prepared by reacting a ketone of formula V with a dialkyl formamide of formula $HCONR_3R_4$ for example in the presence of formic acid.

Compounds of formula I may be prepared by the reduction of compounds of formula VI



VI

in which

(a) Z is a group of formula $—CR_1=NOH$ or an ester or ether thereof to give compounds of formula I in which R_2, R_3 and R_4 are H;

(b) Z is a group of formula $—CR_1=NR_3$ (where R_3 is other than H or CHO) to give compounds of formula I in which

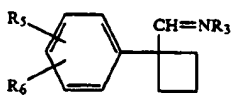
R_2 and R_4 are H;

(c) Z is a group of formula $—CR_1=NY$ in which Y represents a metal-containing moiety derived from an organometallic reagent to give compounds of formula I in which R_2, R_3 and R_4 are H;

Suitable reducing agents for the above reactions include sodium borohydride, sodium cyanoborohydride, or lithium aluminium hydride.

In (c) above Y is preferably MgBr derived from a Grignard reagent or Li derived from an organolithium compound.

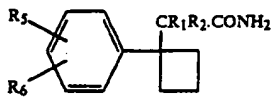
Compounds of formula I may be prepared by the reaction of an organometallic reagent for example a Grignard reagent of formula R_1MgX where X is Cl, Br or I or an organolithium compound of formula R_1Li with an imine of formula VII



VII

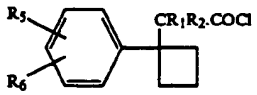
followed by hydrolysis to give a secondary amine of formula I.

Compounds of formula I in which R_3 and R_4 are H may be prepared by the decarboxylative rearrangement, for example using iodosobenzene-bistrifluoroacetate or by a Hofmann reaction using bromine in alkaline solution, of amides of formula VIII



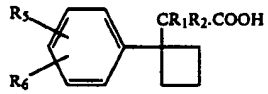
VIII

Compounds of formula I in which R_3 and R_4 are H may be prepared by the decarboxylative rearrangement of acyl azides in the Curtius reaction. The acyl azides may be formed for example by reaction of acid chlorides of formula IX with sodium azide.



IX

Compounds of formula I in which R_3 and R_4 are H may be prepared by a Schmidt reaction in which carboxylic acids of formula X react with hydrazoic acid



X

Compounds of formula I in which R_4 is H may be prepared by hydrolysis of compounds of formula I in which R_4 is CHO, for example by acid hydrolysis.

Compounds of formula I in which R_4 is methyl may be prepared by reduction of compounds of formula I in which R_4 is CHO, for example by lithium aluminium hydride or by sodium bis(2-methoxyethoxy)aluminium hydride.

Compounds of formula I in which one or both of R_3 and R_4 is other than H may be prepared from compounds of formula I in which one or both of R_3 and R_4 are hydrogen by methods which are well known in the art for the conversion of primary to secondary or tertiary amines or for the conversion of secondary to tertiary amines. The following are given as examples of suitable processes:

(a) by alkylating primary amines of formula I to give secondary amines of formula I for example by a process which includes the steps of protecting the primary amine with a protecting group such as trifluoroacetyl, alkylating with an alkyl halide and removing the protecting group for example by hydrolysis;

(b) by alkylating primary amines of formula I, for example, with an alkyl halide to give tertiary amines of formula I in which R_3 and R_4 are the same;

(c) by alkylating secondary amines of formula I, for example, with an alkyl halide to give tertiary amines of formula I in which R_3 and R_4 may be different;

(d) by reacting primary amines of formula I with sodium borohydride and acetic acid to give secondary amines of formula I in which R_3 is ethyl and R_4 is H;

(e) by reacting primary amines of formula I with formaldehyde and formic acid to give tertiary amines of formula I in which both R_3 and R_4 are methyl

(f) by reacting secondary amines of formula I in which R_4 is H with formaldehyde and formic acid to give tertiary amines of formula I in which R_4 is methyl

(g) by formylating primary amines of formula I, for example by reaction with methyl formate, and reducing the resulting formamides, for example with lithium

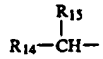
aluminium hydride to give secondary amines of formula I in which R_3 is methyl and R_4 is H;

(h) by formylating secondary amines of formula I, for example by reaction with methyl formate, and reducing the resulting formamides, for example with lithium aluminium hydride to give tertiary amines of formula I in which R_4 is methyl.

(i) by acylating primary amines of formula I, for example by reaction with an acyl chloride of formula $R_{12}COCl$ or an anhydride of formula $(R_{12}CO)_2O$ in which R_{12} is an alkyl, alkenyl or alkynyl group and reducing the resulting amides for example with lithium aluminium hydride to give secondary amines of formula I in which R_3 is $—CH_2R_{12}$ and R_4 is H.

(j) by acylating secondary amines of formula I in which R_4 is H for example by reaction with an acyl chloride of formula $R_{12}COCl$ or an anhydride of formula $(R_{12}CO)_2O$ in which R_{12} is an alkyl, alkenyl or alkynyl group and reducing the resulting amides for example with lithium aluminium hydride to give tertiary amines in which R_4 is CH_2R_{12};

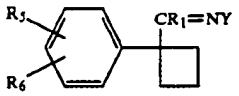
(k) by reacting primary amines of formula I with an aldehyde of formula $R_{13}CHO$ in which R_{13} may be an alkyl group, an alkenyl or alkynyl group or with a ketone of formula $R_{14}COR_{15}$ in which R_{14} and R_{15} which may be the same or different are an alkyl group, alkenyl group, alkynyl group or R_{14} and R_{15} together with carbon atom to which they are attached form an alicyclic ring and reducing the resulting imines or enamines for example with sodium cyanoborohydride or, when R_{13}, R_{14} or R_{15} are not alkenyl or alkynyl, by catalytic hydrogenation to give secondary amines of formula I in which R_3 is $R_{13}CH_2—$ and



respectively;

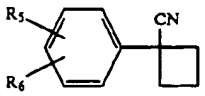
(l) by reacting primary amines of formula I with a non-geminally disubstituted alkane containing 2 or 3 carbon atoms between the carbon atoms carrying the substituents which may be for example halo preferably bromo, or p-toluenesulphonyloxy to give compounds of formula I in which R_3 and R_4 together with the nitrogen to which they are attached form a heterocyclic ring containing no heteroatoms other than the nitrogen atom.

The ketones of formula V may be prepared by the hydrolysis of imines of formula XI



XI

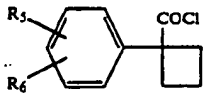
in which Y represents a metal-containing moiety derived from an organometallic reagent. The imines of formula XI may be prepared by the reaction of said organometallic reagent with a cyano compounds of formula XII



XII

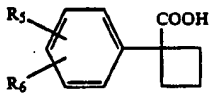
Suitable organometallic reagents include Grignard reagents of formula R_1MgX where X is Cl, Br or I (Y=MgX) and organolithium compounds of formula R_1Li (Y=Li).

Ketones of formula V may be prepared by the reaction of carboxylic acid derivatives such as amides or acid halides with an organometallic reagent for example by the reaction of an acid chlorides of formula XIII



XIII

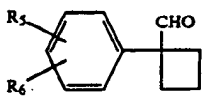
with a Grignard reagent of formula R_1MgX where X is Cl, Br or I at low temperatures or by the reaction of carboxylic acids of formula XIV



XIV

with an organometallic reagent, for example an organolithium compound of formula R_1Li.

Ketones of formula V in which R_1 is alkyl (e.g. methyl) may be prepared by the reaction of a diazoalkane (e.g. diazomethane) with aldehydes of formula XV



XV

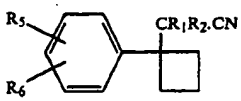
Compounds of formula VI in which Z is a group of formula $—CR_1=NOH$ or ethers or esters thereof may be prepared by the reaction of hydroxylamine or an ether or ester thereof with ketones of formula V.

Compounds of formula VI in which Z is a group of formula $—CR_1=NR_3$ may be prepared by the reaction of amines of formula R_3NH_2 with ketones of formula V.

The preparation of compounds of formula VI in which Z is a group of formula $—CR_1=NY$ has been described above in respect of compounds of formula XI.

Imines of formula VII may be prepared by reaction of amines of formula R_3NH_2 with aldehydes of formula XV.

Amides of formula VIII may be prepared by the reaction of ammonia with carboxylic acid derivatives for example acid chlorides of formula IX or they may be prepared from cyano compounds of formula XVI for example by hydration with aqueous acids or by reaction with hydrogen peroxide in the presence of a base.

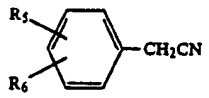


XVI

Carboxylic acids of formula X and XIV may be prepared by the hydrolysis, for example basic hydrolysis, of cyano compounds of formula XVI and XII respectively. Carboxylic acids of formula X may be prepared by the reaction of amides of formula VIII with nitrous

acid. Carboxylic acids of formula XIV may be prepared by the reaction of nitrous acid with the amides formed by (a) the reaction of ammonia with carboxylic acid derivatives for example acid chlorides of formula XIII or (b) by the reaction of cyano compounds of formula XII with hydrogen peroxide in the presence of a base.

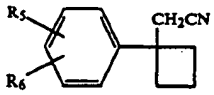
Cyano compounds of formula XII may be prepared by the reaction of cyano compounds of formula XVII



XVII

with a 1,3-disubstituted propane for example 1,3-dibromopropane and a base such as sodium hydride.

Cyano compounds of formula XVIII



XVIII

may be prepared from cyano compounds of formula XII by for example the following series of reactions

(a) hydrolysis of the cyano group to form a carboxylic acid of formula XIV;

(b) reduction of the carboxylic acid for example with lithium aluminium hydride or borane-dimethylsulphide complex to form the corresponding alcohol;

(c) replacement of the hydroxy group of the alcohol by a leaving group for example a p-toluene sulphonyloxy group and

(d) replacement of the leaving group with a cyano group. Cyano compounds of formula XVI in which one or both of R_1 and R_2 are other than H may be prepared from the corresponding cyano compounds of formula XVI in which R_1 and/or R_2 are H, for example by alkylation with an alkyl halide in the presence of a base such as lithium diisopropylamide.

Cyano compounds of formula XVI in which R_2=H may also be prepared by reacting ketones of formula V with a reagent for introducing a cyano group such as p-toluenesulphonylmethyl isocyanide.

Acid chlorides of formula XIII and IX may be prepared by the reaction of carboxylic acids of formula XIV and X respectively with for example thionyl chloride.

Aldehydes of formula XV may be prepared by methods well known to those skilled in the art. The following are given as examples of suitable methods:

(a) by the reduction of cyano compounds of formula XII with for example di-tert-butylaluminium hydride or diisobutylaluminium hydride.

(b) by the reduction of carboxylic acid derivatives, for example

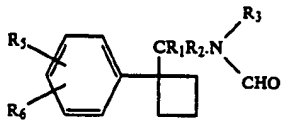
(i) by the reduction of tertiary amides formed by the reaction of secondary amines with acid chlorides of formula XIII for example when the secondary amine is a dialkylamine using lithium diethoxyaluminohydride as reducing agent or when the secondary amine is ethyleneimine using lithium aluminium hydride as the reducing agent,

(ii) by the reduction of acid chlorides of formula XIII for example with lithium tri-tert-butoxyaluminohydride.

(c) by the oxidation of alcohols (prepared by the reduction of carboxylic acids of formula XIV) with, for example, chromium trioxide-pyridine complex in dichloromethane under anhydrous conditions.

Ketones of formula V (except those in which R_5 and R_6 are H and R_1 is methyl or ethyl), the compounds of formula VI (except those in which Z is CR_1=NY and R_5 and R_6 are H and R_1 is methyl and ethyl), the imines of formula VII (except those in which R_5 and R_6 are H), and XI (except those in which R_5 and R_6 are H and R_1 is methyl or ethyl), the amides of formula VIII, the carboxylic acids of formula X (except those in which R_1, R_2, R_5 and R_6 are H), the cyano compounds of formula XVI and the acid chlorides of formula IX (except those in which R_1, R_2, R_5 and R_6 are H) which are described herein as intermediates are novel compounds. Some of the cyano compounds of formula XII and XVII are novel compounds. Such novel compounds form a further aspect of the present invention.

Novel formamides of formula XIX



XIX

are described herein as intermediates, in the preparation of compounds of formula I and such novel formamides form a further aspect of the present invention.

The therapeutic activity of the compounds of formula I has been indicated by assessing the ability of the compounds to reverse the hypothermic effects of reserpine in the following manner. Male mice of the Charles River CD1 strain weighing between 18 and 30 grammes were separated into groups of five and were supplied with food and water ad libitum. After five hours the body temperature of each mouse was taken orally and the mice were injected intraperitoneally with reserpine (5 mg/kg) in solution in deionised water containing ascorbic acid (50 mg/ml). The amount of liquid injected was 10 ml/kg of body weight. Nine hours after the start of the test food was withdrawn but water was still available ad libitum. Twenty-four hours after the start of the test the temperatures of the mice were taken and the mice were given the test compound suspended in a 0.25% solution of hydroxy ethyl cellulose (sold under the trade name Cellosize QP 15000 by Union Carbide) in deionised water at a dose volume of 10 ml/kg of body weight. Three hours later the temperatures of all the mice were again taken. The percentage reversal of the reserpine-induced loss of body temperature is then calculated by the formula:

$$\frac{\text{(Temperature after 27 hrs} - \text{Temperature after 24 hours)} \times 100}{\text{(Temperature after 5 hrs} - \text{Temperature after 24 hours)}}$$

The mean value for each group of five mice was taken at several dose rates to enable a value of the mean dose which causes a 50% reversal (ED50) to be obtained. All the compounds which are the final products of the Examples hereinafter gave values of ED50 of 30 mg/kg or less. It is widely understood by those skilled in the art that this test is indicative of compounds having antidepressant activity in humans.

Table I lists compounds of formula I which gave a value of ED50 in the above test of 10 mg/kg or less.

TABLE I

1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine hydrochloride
N-methyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine hydrochloride
N,N-dimethyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine hydrochloride
1-[1-(4-iodophenyl)cyclobutyl]ethylamine hydrochloride
N-methyl-1-[1-(4-iodophenyl)cyclobutyl]ethylamine hydrochloride
N,N-dimethyl-1-[1-(4-iodophenyl)cyclobutyl]ethylamine hydrochloride
N-methyl-1-[1-(2-naphthyl)cyclobutyl]ethylamine hydrochloride
N,N-dimethyl-1-[1-(4-chloro-3-trifluoromethylphenyl)-cyclobutyl]ethylamine hydrochloride
1-[1-(4-chlorophenyl)cyclobutyl]butylamine hydrochloride
N-methyl-1-[1-(4-chlorophenyl)cyclobutyl]butylamine hydrochloride
N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]butylamine hydrochloride
1-[1-(3,4-dichlorophenyl)cyclobutyl]butylamine hydrochloride
N-methyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]butylamine hydrochloride
N,N-dimethyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]-butylamine hydrochloride
1-[1-(4-biphenylyl)cyclobutyl]butylamine hydrochloride
N,N-dimethyl-1-[1-(4-biphenylyl)cyclobutyl]butylamine hydrochloride
1-[1-(4-chloro-3-fluorophenyl)cyclobutyl]butylamine hydrochloride
N-formyl-1-[1-(4-chloro-3-fluorophenyl)cyclobutyl]-butylamine
1-[1-(3-chloro-4-methylphenyl)cyclobutyl]butylamine hydrochloride
N-formyl-1-[1-phenylcyclobutyl]butylamine
1-[1-(3-trifluoromethylphenyl)cyclobutyl]butylamine hydrochloride
1-[1-(naphth-2-yl)cyclobutyl]butylamine hydrochloride
1-[1-(6-chloronaphth-2-yl)cyclobutyl]butylamine
N-methyl-1-[1-(4-chlorophenyl)cyclobutyl]-2-methylpropylamine hydrochloride
1-[1-(4-chlorophenyl)cyclobutyl]pentylamine hydrochloride
N-methyl-1-[1-(4-chlorophenyl)cyclobutyl]pentylamine hydrochloride
N,N-dimethyl-1-[1-phenylcyclobutyl]-3-methylbutylamine hydrochloride
1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride
N-methyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride
N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride
N-formyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine
N,N-dimethyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride
N-methyl-1-[1-(naphth-2-yl)cyclobutyl]-3-methylbutylamine hydrochloride
N-methyl-1-[1-(3,4-dimethylphenyl)cyclobutyl]-3-methylbutylamine hydrochloride
[1-(4-chlorophenyl)cyclobutyl](cyclopropyl)methylamine hydrochloride
N-methyl-[1-(4-chlorophenyl)cyclobutyl](cyclopentyl)methylamine hydrochloride
[1-(4-chlorophenyl)cyclobutyl](cyclohexyl)methylamine hydrochloride
N-methyl-[1-(4-chlorophenyl)cyclobutyl](cyclohexyl)-methylamine hydrochloride
[1-(3,4-dichlorophenyl)cyclobutyl](cyclohexyl)methylamine hydrochloride
N-methyl-[1-(3,4-dichlorophenyl)cyclobutyl](cyclohexyl)methylamine hydrochloride
[1-(4-chlorophenyl)cyclobutyl](cycloheptyl)methylamine hydrochloride
1-[1-(4-chlorophenyl)cyclobutyl]-2-cyclopropylethylamine hydrochloride
N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-2-cyclohexylethylamine hydrochloride
α-[1-(4-chlorophenyl)cyclobutyl]benzylamine hydrochloride
N-methyl-α-[1-(4-chlorophenyl)cyclobutyl]benzylamine hydrochloride
1-[1-(4-chloro-2-fluorophenyl)cyclobutyl]butylamine
N,N-dimethyl-1-[1-(4-chloro-2-fluorophenyl)cyclobutyl]butylamine hydrochloride
N-ethyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine hydrochloride
N,N-diethyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine hydrochloride

The invention will now be illustrated by the following Examples which are given by way of example only. All compounds were characterised by conventional analytical techniques and gave satisfactory elemental analyses. All melting and boiling points are expressed in degrees Celsius.

EXAMPLE 1

A solution of 3,4-dichlorobenzyl cyanide (25 g) and 1,3-dibromopropane (15 ml) in dry dimethyl sulphoxide (150 ml) was added dropwise under nitrogen to a stirred mixture of sodium hydride (7.5 g) dispersed in mineral oil (7.5 g) and dimethylsulphoxide (200 ml) at a temperature in the range 30° to 35° C. The mixture was stirred at room temperature for two hours and propan-2-ol (8 ml) and then water (110 ml) were added dropwise. The mixture was filtered through a diatomaceous earth sold under the Registered Trade Mark CELITE and the solid residue washed with ether. The ether layer was separated, washed with water, dried and evaporated. 1-(3,4-Dichlorophenyl)-1-cyclobutanecarbonitrile (b.p. 108°–120° C. at 0.15 Hg) was isolated by distillation. This method is a modification of that described by Butler and Pollatz (J.Org.Chem., Vol. 36, No. 9, 1971, p. 1308).

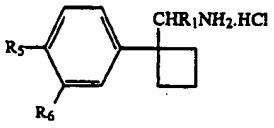
The 1-(3,4-dichlorophenyl)-1-cyclobutanecarbonitrile prepared as above (21.7 g) was dissolved in dry ether (50 ml) and the solution was added under nitrogen to the product of the reaction of gaseous methyl bromide with magnesium turnings (3.9 g) in dry ether (150 ml). The mixture was stirred at room temperature for two hours and then under reflux for two hours. Crushed ice and then concentrated hydrochloric acid (100 ml) were added and the mixture heated under reflux for two hours. The ether layer was separated, washed with water and aqueous sodium bicarbonate, dried and evaporated. 1-Acetyl-1-(3,4-dichlorophenyl)cyclobutane (b.p. 108°–110° at 0.2 mm Hg) was isolated by distillation.

1-Acetyl-1-(3,4-dichlorophenyl)cyclobutane (9.1 g) prepared as above, formamide (6.5 ml) and 98% formic acid (3 ml) were heated at 180° C. for sixteen hours to give N-formyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine. Concentrated hydrochloric acid (20 ml) was added and the mixture heated under reflux for three hours. The solution was then cooled, washed with ether and sodium hydroxide solution added. The product was extracted with ether, and the ether extract washed with water, dried and evaporated. 1-[1-(3,4-Dichlorophenyl)cyclobutyl]ethylamine (b.p. 112°-118° at 0.2 mm Hg) was isolated by distillation. The amine was dissolved in propan-2-ol and concentrated hydrochloric acid and the solution evaporated to dryness to give 1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine hydrochloride (m.p. 185°-195° C.). (Formula I R_1=Me; R_2, R_3 and R_4=H; R_5=4-Cl; R_6=3-Cl).

EXAMPLE 1a

The preparation of N-formyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine (m.p. 124°-125° C.) (Example 1(a) Formula I R_1=Me; R_2=H; R_3=H; R_4=CHO; R_5=4-Cl and R_6=3-Cl) described above was repeated and the product isolated by cooling the reaction mixture and collecting the solid produced by filtration. The formamide was then hydrolysed by concentrated hydrochloric acid in industrial methylated spirit to give the hydrochloride salt of 1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine.

In a similar manner to that described above in Example Ia the following compounds were prepared. The conditions for the hydrolysis of the formamides which were isolated by appropriate methods are shown in the footnotes.



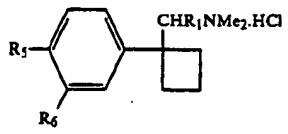
Example	R_1	R_5	R_6	b.p. (free base)	m.p. of HCl salt	Note
1(b)	methyl	Cl	H	107°/1.2 mm Hg		A
1(c)	n-butyl	Cl	H		138-139°	B
1(d)	methyl	I	H		205-207°	C
1(e)	methyl	Cl	CF_3		216-217°	D

A. aqueous HCl/industrial methylated spirit
B. The 1-valeryl-1-(4-chlorophenyl)cyclobutane was prepared in tetrahydrofuran. Hydrolysis was performed using concentrated HCl/industrial methylated spirit.
C. concentrated HCl/diethyleneglycoldimethyl ether (in a similar manner to that described later in Example 12).
D. concentrated HCl/industrial methylated spirit.

EXAMPLE 2

The product of Example 1 (4.04 g), water (0.5 ml) and 98% formic acid (3.6 ml) were mixed with cooling. 37-40% Aqueous formaldehyde (3.8 ml) was added and the solution was heated at 85°-95° C. for five hours. The solution was evaporated to dryness and the residue acidified with concentrated hydrochloric acid and the water removed by repeated addition of propan-2-ol followed by evaporation in vacuo. Crystals of N,N-dimethyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine hydrochloride (m.p. 211°-213° C.) (Formula I R_1=Me; R_2=H; R_3, R_4=Me; R_5=4-Cl; R_6=3-Cl) were isolated.

In a similar way to that described above the compounds of Example 1(b) and 1(d) were converted into the compounds listed below.



Example	Starting Material	R_1	R_5	R_6	m.p. of HCl salt	b.p. of free base
2(a)	1(b)	methyl	Cl	H		98-100°/0.5 mm
2(b)	1(d)	methyl	I	H	260-261°	

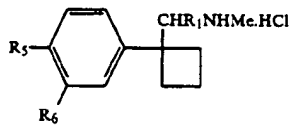
EXAMPLE 3

In a similar manner to that described above in Examples 1 and 2 N,N-dimethyl-1-[1-(4-biphenylyl)cyclobutyl]ethylamine hydrochloride (m.p. 196°-197° C.) was prepared. (Formula I R_1=Me; R_2=H; R_3, R_4=Me; R_5=4-phenyl and R_6=H).

EXAMPLE 4

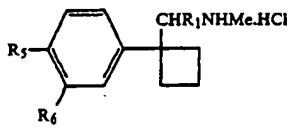
1-Acetyl-1-(3,4-dichlorophenyl)cyclobutane (15 g) prepared as described in Example 1, N-methylformamide (47.5 ml) 98% formic acid (10.3 ml) and a 25% aqueous solution of methylamine (1.5 ml) were mixed and heated with stirring at 170°-180° for eight hours. The mixture was cooled and extracted with ether. The ether extract was washed, dried and evaporated to yield a light yellow oil which was heated under reflux with concentrated hydrochloric acid (50 ml) for two hours. Industrial methylated spirit (IMS) (50 ml) was added and the mixture heated under reflux for sixteen hours. The mixture was then cooled to 0° C. and the white precipitate collected by filtration, washed with acetone and dried. The product, N-methyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine hydrochloride, had a melting point of 254° to 256° C. (Formula I R_1=Me; R_2=H; R_3=Me; R_4=H; R_5=4-Cl and R_6=3-Cl).

In a similar manner to that described above the following compounds of formula I were prepared



Example	R_1	R_5	R_6	b.p. of amine	m.p. of HCl salt	Note
4(a)	Me	Cl	H	98-100°/0.15 mm	240-241°	
4(b)	Me	H	Cl		269-272°	
4(c)	Me	Br	H	96-98°/0.1 mm		
4(d)	Me	H	Br		251-255°	
4(e)	Me	CF_3	H		219-221°	
4(f)	Me	H	CF_3		225-228°	
4(g)	Me	—(CH=CH)$_2$—			254-257°	
4(h)	Me	Cl	CF_3		198-200°	
4(i)	Et	Cl	H		238-240°	
4(j)	Pr	Cl	H		228-229°	A
4(k)	Bu	Cl	H		152-153°	A

-continued



Example	R_1	R_5	R_6	b.p. of amine	m.p. of HCl salt	Note
4(l)	Me	I	H		242–243°	

Note A
The starting ketone was prepared in tetrahydrofuran as reaction solvent in place of ether.

EXAMPLE 5

A mixture of 70% aqueous ethylamine (50 ml) and water (100 ml) was gradually mixed with a mixture of 98% formic acid (50 ml) and water (100 ml) to give a neutral solution which was evaporated at 100° C./100 mm Hg until 180 ml of water had been collected. The residue was heated to 140° C. and 1-acetyl-1-(4-chlorophenyl)cyclobutane (10.4 g) prepared in a similar manner to that described in Example 1 for 1-acetyl-1-(3,4-dichlorophenyl)cyclobutane and 98% formic acid (10 ml) were added. The mixture was heated on an oil bath at a temperature of 180°–200° C. for sixteen hours. The mixture was distilled until an internal temperature of 170° C. was obtained and this temperature was maintained for two hours. Any volatile material was removed by distillation at 160° C./20 mm and the residue heated under reflux with concentrated hydrochloric acid (15 ml) and industrial methylated spirit (IMS) (15 ml) for three hours. The IMS was evaporated on a rotary evaporator and the residue washed with ether. The aqueous phase was brought to pH 12 with sodium hydroxide and extracted with ether. The ether extract was dried and on evaporation yielded a residue which was treated with aqueous hydrochloric acid to give N-ethyl-1-[1-(4-chlorophenyl)cyclobutyl]ethylamine hydrochloride (m.p. 203°–205° C.) (Formula I R_1=Me; R_2=H; R_3=Et; R_4=H; R_5=4-Cl; R_6=H).

EXAMPLE 6

1-(4-Chlorophenyl)-1-cyclobutanecarbonitrile (15 g) prepared in a similar manner to the 1-(3,4-dichlorophenyl)cyclobutanecarbonitrile of Example 1 in dry ether (50 ml) was added to the product of the reaction between magnesium turnings (3.18 g) and propyl bromide (15.99 g) in dry ether (50 ml). The ether was replaced by tetrahydrofuran and the mixture heated with stirring under reflux for eighteen hours. The mixture was cooled and ice and then concentrated hydrochloric acid (52 ml) added. The resulting mixture was stirred under reflux for ten hours and extracted with ether. The ether extract yielded a residue from which 1-butyryl-1-(4-chlorophenyl)cyclobutane (b.p. 106°–108°/0.3 mm Hg) was distilled.

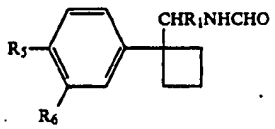
A mixture of the ketone produced as described above (21 g) and 98% formic acid (6 ml) was added over a period of one and a half hours to formamide (15 ml) at 160° C. After completion of the addition the temperature was raised to 180° to 185° C. and maintained in this range for five hours. The mixture was cooled and extracted with chloroform to yield a thick gum which on heating with petroleum ether (b.p. 60°–80°) gave a colourless solid which was recrystallised from petroleum ether (b.p. 60°–80°) to yield N-formyl-1-[1-(4-chlorophenyl)cyclobutyl]butylamine (m.p. 97.5° to 98.5° C.) (Formula I R_1=propyl; R_2=H; R_3=H; R_4=CHO; R_5=4-Cl; R_6=H).

EXAMPLE 7

A solution of 1-(3,4-dichlorophenyl)-1-cyclobutanecarbonitrile prepared as described in Example 1 (35.2 g) in ether (100 ml) was added to a solution of propyl magnesium bromide prepared by the reaction of propyl bromide (32 g) with magnesium turnings (6.36 g) in ether (100 ml). The ether was replaced by dry toluene and the mixture heated under reflux for one hour. Water (200 ml) and then concentrated hydrochloric acid (120 ml) were added and the mixture heated under reflux for one hour. The reaction mixture was extracted with ether and after washing and drying the extract yielded a residue from which 1-butyryl-1-(3,4-dichlorophenyl)cyclobutane (b.p. 120°–128° C. at 0.25 mm) was distilled.

The ketone produced as described above (37.0 g) and 98% formic acid (9 ml) were added to formamide (23.5 ml) at 170° C. and the temperature kept at 175°–180° C. for five hours. A further portion of formic acid (4.5 ml) was added and the mixture was maintained at 175°–180° C. for a further fifteen hours. The mixture was extracted with ether which on evaporation gave a thick oil which was crystallised from petroleum ether (b.p. 60°–80°) to give N-formyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]-butylamine having a melting point of 103°–105° C. (Formula I R_1=propyl; R_2=H; R_3=H; R_4=CHO; R_5=4-Cl and R_6=3-Cl).

In a similar manner to that described above the following compounds were made



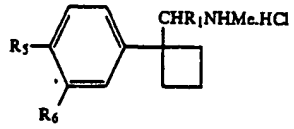
Example	R_1	R_5	R_6	m.p. (°C.)
7(a)	isobutyl	Cl	H	110–112°
7(b)	propyl	Cl	F	115–116°
7(c)	phenyl	Cl	H	94–96°
7(d)	propyl	H	H	98–102°

EXAMPLE 8

The product of Example 7 (4.0 g) in dry tetrahydrofuran (25 ml) was added rapidly to a stirred mixture of lithium aluminium hydride (1.4 g) in dry tetrahydrofuran (25 ml) under nitrogen. The mixture was heated under reflux for five hours and then cooled. Water (15 ml) and then 10% sodium hydroxide solution (3 ml) were added and the mixture filtered through diatomaceous earth sold under the Registered Trade Mark CELITE. The product was extracted into ether, back extracted into 5N hydrochloric acid and the aqueous layer was basified and extracted with ether. The ether extract yielded an oil which was dissolved in propan-2-ol (5 ml) and concentrated hydrochloric acid was added to pH 2. Evaporation of the resulting solution gave a white solid which was collected, washed with acetone and dried. The product was N-methyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]butylamine hydrochloride

and had a melting point of 234°-235° C. (Formula I R_1=propyl; R_2=H; R_3=H; R_4=Me; R_5=4-Cl and R_6=3-Cl).

In a similar manner to that described above the following compounds were prepared

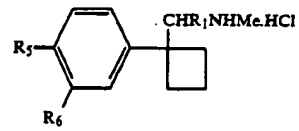


Example	R_1	R_5	R_6	m.p. (°C.)
8(a)	phenyl	Cl	H	275-278°
8(b)	propyl	Cl	H	223-228°

EXAMPLE 9

The product of Example 7 (10 g) in solution in ether (50 ml) was added to a 70% toluene solution of sodium bis(2-methoxyethoxy)aluminium hydride sold under the trade mark Red-al (40 ml) at a temperature in the range 25° to 30° C. The mixture was stirred at this temperature for four hours. Water (25 ml) was added dropwise with cooling and the mixture filtered through diatomaceous earth (CELITE). Aqueous NaOH was added and an ether extraction performed. The ether extract was washed with water and back extracted with 5N hydrochloric acid. A white solid (m.p. 232°-235° C.) appeared at the interface which was collected. Base was added to the aqueous phase and a further ether extraction performed. Evaporation of the ether extract yielded an oil which was dissolved in propan-2-ol (5 ml) and concentrated hydrochloric acid added to pH 2. Evaporation to dryness gave a white solid (m.p. 233°-236° C.). The white solids were combined and recrystallised from propan-2-ol to yield N-methyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]butylamine hydrochloride (m.p. 236°-237° C.) (Formula I R_1=propyl; R_2=H; R_3=H; R_4=Me; R_5=4-Cl and R_6=3-Cl).

In a similar manner to that described above the following compounds were prepared. Where the formyl starting material was insoluble in ether, a solution of the reducing agent was added to a stirred suspension of the formyl compound. As the size of the group R_1 is increased the hydrochloride salts of the desired compounds become less soluble in the aqueous phase and more soluble in the organic phase so that appropriate modifications in the isolation procedure are required as will be apparent to those skilled in the art.



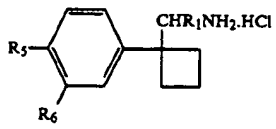
Example	R_1	R_5	R_6	m.p.
9(a)	isopropyl	Cl	H	257-259°
9(b)	sec-butyl	Cl	H	209-212°
9(c)	isobutyl	Cl	H	225-233°
9(d)	cyclopentyl	Cl	H	252-256°
9(e)	n-hexyl	Cl	H	117-118°
9(f)	4-methoxyphenyl	Cl	H	264-266°
9(g)	3-methoxyphenyl	Cl	H	254-255°
9(h)	2-methoxyphenyl	Cl	H	149-153°
9(i)	cyclohexyl	Cl	H	170-172°
9(j)	isobutyl	—(CH=CH)$_2$—		256-259°
9(k)	cyclohexyl	Cl	Cl	223-224°
9(l)	isobutyl	Me	Me	(1)
9(m)	propyl	OMe	H	173-175°
9(n)	methyl	phenyl	H	116-118°

(1) Boiling point of free base >150° at 1.0 mm Hg.

EXAMPLE 10

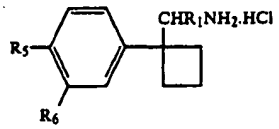
The product of Example 7 (4 g), diethyleneglycoldimethyl ether (25 ml), water (10 ml) and concentrated hydrochloric acid (10 ml) were mixed and heated under reflux for nine hours. The solution was washed with ether and aqueous NaOH added before an ether extraction was performed. The ether extract was washed with brine and water and yielded an oil on evaporation. The oil (B 3.19 g) was dissolved in a mixture of propan-2-ol (4 ml) and ether (20 ml) and concentrated hydrochloric acid (1.5 ml) added. The solvent was evaporated in vacuo. Repeated dissolution in industrial methylated spirit and evaporation in vacuo gave a gum which solidified on warming in vacuo. The product was recrystallised from petroleum ether (b.p. 100°-120° C.) and had a melting point of 201°-203° C. The product was 1-[1-(3,4-dichlorophenyl)cyclobutyl]butylamine hydrochloride (Formula I R_1=propyl; R_2=H; R_3, R_4=H; R_5=4-Cl and R_6=3-Cl).

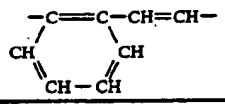
In a similar manner to that described above the following compounds were prepared. As the size of the group R_1 is increased the hydrochloride salts of the desired compounds become less soluble in the aqueous phase and more soluble in the organic phase so that appropriate modifications in the isolation procedure are required as will be apparent to those skilled in the art.



Example	R_1	R_5	R_6	m.p.
10(a)	isopropyl	Cl	H	200-202°
10(b)	sec-butyl	Cl	H	178-179°
10(c)	isobutyl	Cl	H	163-165°
10(d)	cyclopentyl	Cl	H	185-210°(dec)
10(e)	phenyl	Cl	H	271-276°
10(f)	4-methoxyphenyl	Cl	H	214-219°
10(g)	cyclohexyl	Cl	H	206-210°
10(h)	isobutyl	H	H	210-212°

-continued



Example	R_1	R_5	R_6	m.p.
10(i)	cyclopropyl	Cl	H	204–206°
10(j)	propyl	Ph	H	235–236°
10(k)	propyl	Me	Cl	214–217°
10(l)	propyl	$-(CH=CH)_2-$		157–159°
10(m)	cycloheptyl	Cl	H	156–162°
10(n)	cyclohexyl	Cl	Cl	215°
10(p)	methyl	Cl	F	215–217°
10(q)	propyl	OMe	H	178–179°
10(r)	propyl	Cl	F	186–188°
10(s)	propyl	Cl	H	174–175°
10(t)	cyclohexylmethyl	Cl	H	148–150°
10(u)	cyclopropylmethyl	Cl	H	184–185°
10(v)	propyl	$-CH=CH-CCl=CH-$		(a)
10(w)	propyl	H	CF_3	126–128°
10(x)	4-fluorophenyl	Cl	H	279°
10(y)(b)	methyl			248–262°

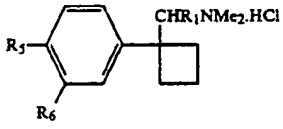
(a) boiling point of free base 168° C./0.05 mm Hg.
(b) diethyleneglycoldimethyl ether replaced by ethyleneglycoldimethyl ether.

In a similar manner to that described above, 1-[1-(4-chloro-2-fluorophenyl)cyclobutyl]butylamine (b.p. 99° C./0.05 mm). (Formula I R_1=propyl; R_2, R_3 and R_4=H; R_5=4-Cl; R_6=2-F), 1-[1-(2-fluorophenyl)cyclobutyl]butylamine hydrochloride (m.p. 175°–177° C.). (Formula I R_1=propyl; R_2, R_3, R_4, R_5=H and R_6=2-F) and 1-[1-(4-chloro-2-methyl)cyclobutyl]butylamine hydrochloride (m.p. 188°–190° C.) (Formula I R_1=propyl; R_2, R_3 and R_4=H; R_5=4-Cl and R_6=2-Me) were prepared as Examples 10(z), 10(aa) and 10(bb) respectively.

EXAMPLE 11

The product of Example 10(c) (3.3 g) in the form of the free base, formic acid (2.99 g) and water (1 ml) were mixed with cooling. 37–40% Aqueous formaldehyde (3.93 ml) was added and the mixture heated for eighteen hours at a temperature of 85°–95° C. Excess dilute hydrochloric acid was added and the solution evaporated to dryness. The residue was basified with 5N sodium hydroxide solution and the product was extracted into ether. Evaporation of the ether yielded a pale yellow oil which was dissolved in a mixture of propan-2-ol (4 ml) and ether (20 ml) and concentrated hydrochloric acid (2 ml) was added dropwise. The solution was evaporated and the residue dissolved repeatedly in ethanol and evaporated in vacuo to give a gum which was triturated with petroleum ether (b.p. 60°–80°) to yield a yellow solid which was recrystallised from acetone. The product was N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride (m.p. 195°–197° C.). (Formula I R_1=isobutyl; R_2=H; R_3, R_4=Me; R_5=4-Cl; R_6=H).

In a similar manner to that described above the following compounds of Formula I were prepared



Example	Starting Material	R_1	R_5	R_6	m.p.
11(a)	10(b)	isobutyl	H	H	195–198°
11(b)	10(j)	propyl	Ph	H	194–196°
11(c)	10(n)	cyclohexyl	Cl	Cl	227–228°
11(d)	10(q)	propyl	OMe	H	187–188°
11(e)	10(s)	propyl	Cl	H	194–196°
11(f)	10(t)	cyclohexylmethyl	Cl	H	194–196°
11(g)	10(u)	cyclopropylmethyl	Cl	H	165–167°
11(h)	10(v)	propyl	$-CH=CH-CCl=CH-$		(a)
11(i)	—	isobutyl	Cl	Cl	225–226°
11(j)	10(x)	4-fluorophenyl	Cl	H	234°
11(k)	—	propyl	isopropyl	H	211–213°

(a) boiling point of free base <250° C./0.05 mm Hg.

EXAMPLE 11(1)

In a similar manner to that described above N,N-dimethyl-1-[1-(4-chloro-2-fluorophenyl)cyclobutyl]-butylamine hydrochloride (m.p. 183°) was prepared. (Formula I R_1=propyl; R_2=H; R_3, R_4=Me; R_5=4-Cl; R_6=2-F).

EXAMPLE 12

The product of Example 7 (8.3 g), diethyleneglycol-dimethyl ether (50 ml), water (20 ml) and concentrated hydrochloric acid (20 ml) were mixed and heated under reflux for sixteen hours. The mixture was poured into water aqueous NaOH was added and the product extracted into ether. Evaporation gave a dark oil. A sample of this oil (7.9 g), water (0.7 ml) and formic acid (6.5 ml) were mixed and formaldehyde (6.5 ml) added. The mixture was heated under reflux for three hours and then concentrated hydrochloric acid (10 ml) and propan-2-ol (10 ml) were added. Evaporation to dryness gave N,N-dimethyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]butylamine hydrochloride (m.p. 195°-196°) as a white solid (Formula I R_1=propyl; R_2=H; R_3, R_4=Me; R_5=4-Cl and R_6=3-Cl).

EXAMPLE 13

1-(4-Chlorophenyl)-1-cyclobutanecarbonitrile (37.6 g) prepared in a similar manner to the 1-(3,4-dichlorophenyl)-1-cyclobutanecarbonitrile described in Example 1 was added to a solution of potassium hydroxide (32.4 g) in diethyleneglycol (370 ml) and the mixture heated under reflux for three and a half hours. The reaction mixture was poured into an ice/water mixture and the resulting solution was washed with ether. The aqueous layer was added to a mixture of concentrated hydrochloric acid (100 ml) and ice and the resulting precipitate of 1-(4-chlorophenyl)-1-cyclobutanecarboxylic acid (m.p. 86°-88°) collected, washed with water and dried.

A solution of the acid (10.5 g) prepared as above in tetrahydrofuran (150 ml) was added dropwise under nitrogen to a stirred suspension of lithium aluminium hydride (2 g) in tetrahydrofuran (150 ml). The mixture was stirred under reflux for two hours and water added. The mixture was filtered through diatomaceous earth (CELITE-RTM) and the product extracted into ether. After washing with water and drying, the ether was evaporated to give a residue which was recrystallised from petroleum ether (b.p. 60°-80°). The product was 1-[1-(4-chlorophenyl)cyclobutyl]methyl alcohol (m.p. 60°-62°C.).

A solution of the alcohol prepared as described above (60 g) in pyridine (52 ml) was added dropwise to a solution of p-toluenesulphonylchloride (60 g) in pyridine (100 ml) cooled in ice. The temperature was allowed to rise to room temperature and remain there for eighteen hours. 1-[1-(4-Chlorophenyl)cyclobutyl]-methyl p-toluene sulphonate (m.p. 99°-100° C.) was precipitated by pouring the reaction mixture into a mixture of ice and concentrated hydrochloric acid (200 ml).

A solution of the sulphonate compound (97 g) prepared as described above and sodium cyanide (16.6 g) in dimethyl sulphoxide (370 ml) was heated on a steam bath for eighteen hours. The mixture was poured into water and extracted with ether. After washing and drying the ether was evaporated to leave a solid residue of 2-[1-(4-chlorophenyl)cyclobutyl]acetonitrile (m.p. 63°-65° C.).

A solution of di-isopropylamine (16.5 g) in dry tetrahydrofuran (50 ml) was stirred under nitrogen at a temperature of 0° C. and a 1.6M solution of n-butyllithium in hexane (100 ml) added dropwise. The reaction mixture was stirred for 30 minutes and then cooled to −78° C. A solution of 2-[1-(4-chlorophenyl)cyclobutyl-]acetonitrile (9.5 g) prepared as described above in dry tetrahydrofuran (25 ml) was added dropwise. The temperature of the mixture was allowed to rise to 0° C. and the mixture was stirred for ten minutes before a solution of methyl iodide (10 ml) in tetrahydrofuran (10 ml) was added. Tetrahydrofuran (75 ml) was added to give a homogeneous solution and a further solution of methyl iodide (4 ml) in tetrahydrofuran (10 ml) added. The mixture was stirred at ambient temperature for two hours and then water (50 ml) added. The aqueous phase was washed with ether and the ether combined with the organic phase of the reaction mixture. The combined organic phases were washed three times with 5N hydrochloric acid, three times with water, dried and evaporated to yield an oil which solidified and was recrystallised from industrial methylated spirit to give 2-[1-(4-chlorophenyl)cyclobutyl]-2-methylpropionitrile (m.p. 73°-75° C.).

The nitrile prepared above (4 g) was heated under reflux with potassium hydroxide (8 g) in diethyleneglycol (40 ml) for 24 hours. The reaction mixture was cooled, added to water (50 ml) and the aqueous phase washed twice with ether. The aqueous phase was acidified with 5N hydrochloric acid and extracted with three portions of ether. The combined ether extracts were washed with water, dried and evaporated to give a white solid which was recrystallised from petroleum ether (b.p. 60°-80°) to give 2-[1-(4-chlorophenyl)cyclobutyl]-2-methylpropionic acid (m.p. 95°-110° C.).

Oxalyl chloride (10 ml) was added to the acid (2 g) prepared as above and after the initial effervesence had subsided the mixture was heated under reflux for one hour. Excess oxalyl chloride was removed by distillation and the residual oil added to concentrated aqueous ammonia (75 ml). An oily solid formed which was extracted into ethyl acetate. The extract was washed with water, dried and evaporated to give 2-[1-(4-chlorophenyl)cyclobutyl]-2-methyl propionamide.

The amide prepared as above (1.34 g) was dissolved in a mixture of acetonitrile (8 ml) and water (8 ml) and iodosobenzene bistrifluoroacetate (3.4 g) added and the mixture stirred at ambient temperature for five and a half hours. Water (75 ml) and concentrated hydrochloric acid (8 ml) were added and the mixture extracted with ether. The ether extract was washed with 5N hydrochloric acid and the aqueous phase basified and extracted with further portions of ether which were dried and evaporated to give an oil. The oil was dissolved in petroleum ether (b.p. 80°-100°) and dry hydrogen chloride gas passed through the solution. 1-[1-(4-Chlorophenyl)cyclobutyl]-1-methylethylamine hydrochloride (m.p. 257°-259° C.) was collected by filtration (Formula I R_1, R_2=Me; R_3, R_4=H; R_5=4-Cl; R_6=H).

EXAMPLE 4

The product of Example 4(h) (3.4 g) was mixed with anhydrous sodium formate (0.72 g), 98% formic acid (10 ml) and 37–40% aqueous formaldehyde solution (5 ml) and the mixture heated at a temperature of 85°-95°

C. for sixteen hours. The mixture was diluted with water (50 ml) and basified to pH 10 with aqueous sodium hydroxide solution. The basic aqueous solution was extracted with ether, washed with water and dried with magnesium sulphate. Dry hydrogen chloride gas was bubbled through the ether extract to give a white precipitate of N,N-dimethyl-1-[1-(4-chloro-3-trifluoromethylphenyl)cyclobutyl]ethylamine hydrochloride (m.p. 246°-247° C.) (Formula I R_1=Me; R_2=H; R_3, R_4=Me; R_5=4-Cl and R_6=3-CF_3).

EXAMPLE 15

The production of salts of the compounds of the invention is illustrated by the following Examples in which equimolar amounts of the base and the acid were taken up in a solvent. The salt was then obtained from the solution by conventional techniques.

Example	Base	Acid	Solvent	m.p. of salt
15(a)	10(s)	citric	aqueous acetone	158–160°
15(b)	10(s)	maleic	ether	155–157°
15(c)	10(s)	succinic	ether	152–155°
15(d)	2	L(+)tartaric	I.M.S.	150–153°
15(e)	Note (a)	citric	ether/methanol	163–164° (dec)

(a) The base was 1-[1-(3,4-dimethylphenyl)cyclobutyl]-3-methylbutylamine prepared in a similar manner to that described in Example 10.

EXAMPLE 16

A solution of bromobenzene (15.7 g) in ether (50 ml) was added dropwise with cooling to magnesium turning (2.4 g) under an atmosphere of nitrogen. A solution of 1-(4-chlorophenyl)-cyclobutanecarbonitrile (19.1 g) prepared in a similar manner to that described in Example 1 for the 1-(3,4-dichlorophenyl)cyclobutane carbonitrile in ether (50 ml) was added and the ether replaced by dry toluene (130 ml). The reaction mixture was heated on a steam bath for one hour. A sample (20 ml) of the resulting solution was added to a solution of sodium borohydride (1 g) in diethyleneglycoldimethyl ether (60 ml) and the mixture was stirred for one and a half hours. Water (60 ml) was added slowly and the aqueous layer extracted with toluene. The toluene extracts were washed with water, dried and evaporated to give a residue which was dissolved in methanol (50 ml). 6N Hydrochloric acid (5 ml) was added and the solution filtered and evaporated. Trituration with dry acetone gave α-[1-(4-chlorophenyl)cyclobutyl]benzylamine hydrochloride (m.p. 277°-279° C.) (Formula I R_1=Ph; R_2=H; R_3, R_4=H; $R_5$4-Cl; R_6=H).

EXAMPLE 17

Methyl formate (62 ml) was added dropwise to isopropylamine (85.5 ml) with stirring at a rate which maintained gentle reflux conditions. Stirring was continued for two hours after the addition. Methanol was distilled off at 100° C. and N-isopropylformamide (b.p. 108°-109° C./25 mm Hg) obtained by distillation.

1-Acetyl-1-(4-chlorophenyl)cyclobutane (10.4 g) prepared in a similar manner to that described in Example 1 for 1-acetyl-1-(3,4-dichlorophenyl)cyclobutane and 98% formic acid (5 ml) were added to N-isopropylformamide (43.5 g) and the mixture heated at 180° C. for four hours. Excess starting material was distilled off under reduced pressure (20 mm Hg) to leave a viscous residue which was heated under reflux with concentrated hydrochloric acid (30 ml) for six hours. The reaction mixture was washed with ether until a colourless solution was obtained. The aqueous phase awas basified, extracted with ether, dried and evaporated to give an oil which was dissolved in 5N hydrochloric acid. On evaporation a yellow oil was obtained which was triturated with petroleum ether (b.p. 62°-68° C.) to give N-isopropyl-1-[1-(4-chlorophenyl)cyclobutyl]ethylamine hydrochloride (m.p. 170°-174° C.) (Formula I R_1=Me; R_2=H; R_3=isopropyl; R_4=H; R_5=4-Cl; R_6=H).

EXAMPLE 18

1-Acetyl-1-(3,4-dichlorophenyl)cyclobutane (7.0 g) prepared as described in Example 1 was slowly added to a mixture of pyrrolidine (25 ml) and 98% formic acid (15 ml) heated to 130°-135° C. for five hours. The mixture was stirred and heated at 160°-165° C. for sixteen hours. After cooling the mixture was poured into 5N hydrochloric acid (200 ml). The solution was washed with ether, basified with aqueous sodium hydroxide solution and extracted with ether. The ether extract was washed with water, dried and hydrogen chloride gas was passed into the extract which was then evaporated to dryness. The residue was triturated with dry ether to give a solid which was recrystallised from propan-2-ol to give N-1-[1-(3,4-dichlorophenyl)cyclobutyl]ethyl pyrrolidine hydrochloride (m.p. 233°-235° C.) (Formula I R_1=Me; R_2=H; R_3 and R_4 together with the nitrogen to which they are attached form a pyrrolidine ring; R_5=4-Cl and R_6=3-Cl).

EXAMPLE 19

1-(4-Chlorophenyl)-1-cyclobutane carboxylic acid (10.5 g) prepared as described in Example 13 was heated under reflux with thionyl chloride (20 ml) for 2½ hours. Excess thionyl chloride was evaporated off and the acid chloride of the above acid distilled (b.p. 82°-96°/0.2 mm Hg).

A solution of the acid chloride (23.0 g) in dry tetrahydrofuran (100 ml) was added slowly to the product of the reaction of magnesium turnings (3.0 g) and ethyl bromide (12.0 g) in dry tetrahydrofuran at a temperature of −70° to −60° C. The temperature was kept at −60° C. for an hour and was then allowed to rise to 0° C. Water (50 ml) was added followed by 5N hydrochloric acid (150 ml) with cooling. The reaction mixture was extracted with ether, washed with water, sodium bicarbonate solution, dried. The solvent was removed by evaporation and 1-propionyl-1-(4-chlorophenyl)cyclobutane obtained by distillation (b.p. 96°-104° C./0.25 mm).

The ketone produced above was converted to N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutylpropylamine hydrochloride (m.p. 213°-215° C.) in a similar manner to that described in Example 12 (Formula I R_1=Et; R_2=H; R_3, R_4=Me; R_5=4-Cl; R_6=H).

EXAMPLE 20

1-Acetyl-1-(4-chlorophenyl)cyclobutane (61 g prepared in a similar manner to that described in Example 1 for 1-acetyl-1-(3,4-dichlorophenyl)cyclobutane, platinum oxide (0.75 g), 33% solution of methylamine in ethanol (60 g) and ethanol (30 ml) were charged into an autoclave. The autoclave was filled with hydrogen and maintained at about 60° C. and 20 bar pressure for ten hours. The reaction mixture was filtered through charcoal and the solids washed with absolute alcohol. The solvents were removed by evaporation and a sample of

the residue (10 g) was shaken with 2M hydrochloric acid (50 ml) and ether (50 ml). The aqueous layer was basified and extracted with ether. The ether extract yielded a liquid on evaporation which was distilled (109° C./0.3 mm Hg) to give N-methyl-1-[1-(4-chlorophenyl)cyclobutyl]ethylamine (Formula I R_1=Me; R_2=H; R_3=Me; R_4=H; R_5=4-Cl and R_6=H).

EXAMPLE 21

Sodium borohydride (2.0 g) was added to solution of 1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine (1.5 g prepared by treating the product of Example 1 with aqueous sodium hydroxide) in glacial acetic acid (30 ml). The mixture was heated at 95°–100° C. for sixteen hours and then cooled. Aqueous sodium hydroxide solution was added and the reaction mixture extracted with ether. The ether extract was shaken with 5N hydrochloric acid and the aqueous layer was washed with ether, basified and extracted with ether. Hydrogen chloride gas was passed into the ether extract which was evaporated to dryness. Trituration with the acetone gave N-ethyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine hydrochloride (m.p. 211°–212° C.). (Formula I R_1=Me; R_2=H; R_3=Et; R_4=H; R_5=4-Cl and R_6=3-Cl.)

EXAMPLE 22

A mixture of N-ethyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine (0.5 g prepared by treating the product of Example 21 with aqueous sodium hydroxide) and acetic anhydride (1 ml) was heated at 40°–45° C. for thirty minutes. The reaction mixture was basified and extracted with ether. The ether extract was washed, dried and evaporated to give N-acetyl-N-ethyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine as an oil.

This oil was dissolved in tetrahyrofuran (10 ml) and borane-dimethylsulphide complex (0.5 ml) added dropwise. The reaction mixture was stirred at room temperature for two hours and then heated to 35°–40° C. for thirty minutes. After cooling the reaction mixture was basified and extracted with ether. Hydrogen chloride gas was passed into the dried ether extract which was evaporated to dryness. Trituration with ether gave N,N-diethyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine hydrochloride (m.p. 199°–201° C.). (Formula I R_1=Me; R_2=H; R_3, R_4=Et; R_5=4-Cl and R_6=3-Cl.)

EXAMPLE 23

A mixture of 1-acetyl-1-(3,4-dichlorophenyl)cyclobutane (2.2 g) prepared as described in Example 1, ammonium acetate (7 g), sodium cyanoborohydride (0.4 g) and methanol (28 ml) was stirred at room temperature for four days. The reaction mixture was poured into a mixture of ice and water and the resulting mixture extracted with ether. The ether extract was washed with water, dried and the ether removed to leave 1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine as an oil which was identified by standard analytical techniques as the compound of Example 1 in the form of its free base.

EXAMPLE 24

A mixture of 1-acetyl-1-(3,4-dichlorophenyl)cyclobutane (4.86 g) prepared as described in Example 1, hydroxylamine hydrochloride (1.6 g), sodium acetate trihydrate (3.3 g), industrial methylated spirit (15 ml) and water (2 ml) was heated under reflux for twenty hours. The cooled reaction mixture was poured into water and the oil which separated was cooled to give a solid which was recrystallised from industrial methylated spirit to give 1-acetyl-1-(3,4-dichlorophenyl)cyclobutane oxime (m.p. 120°–121° C.).

A solution of the oxime prepared above (4.0 g) in ether (50 ml) was added slowly to a stirred suspension of lithium aluminium hydride (0.9 g) in ether (50 ml) under nitrogen. The mixture was heated uner reflux for one hour and, after cooling, water and then a 20% aqueous solution of Rochelle's salt (potassium sodium tartrate tetrahydrate) (27 ml) and a 10% aqueous solution of sodium hydroxide (6 ml) added. The reaction mixture was stirred for one hour and then continuously extracted with ether during eighteen hours. The ether extract was dried and the ether removed to leave a solid from which 1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine was separated by high pressure liquid chromatography. The product was identified by standard analytical techniques as the compound of Example 1 in the form of its free base.

EXAMPLE 25

A 1M solution of diisobutylaliminohydride in hexane (200 ml) was added under nitrogen to a solution of 1-phenyl-1-cyclobutane carbonitrile (31.4 g) in ether (100 ml) at a temperature below −30° C. The temperature was maintained below 0° C. for thirty minutes and 5N hydrochloric acid (200 ml) at a temperature of −10° C. added. The reaction mixture was washed with petroleum ether (b.p. 60°–80° C.) and then warmed to 40° C. The reaction mixture was extracted with petroleum ether (b.p. 60°–80° C.) and the extract dried and evaporated to yield 1-phenyl-1-cyclobutane-carbaldehyde as an oil.

Methylamine was bubbled through a solution of the aldehyde (9.4 g) prepared as above in toluene (100 ml) whilst the temperature of the reaction mixture was maintained below 0° C. Magnesium sulphate (20 g) which had been dried over a flame and then cooled under nitrogen was added to the reaction mixture which was left for sixteen hours at room temperature before being filtered. The toluene was then removed by evaporation and the residue dissolved in ether (50 ml). This solution was added to a solution of propyllithium prepared by slowly adding excess propyl bromide (12.8 g) to a suspension of lithium (1.26 g) in ether (50 ml). The resulting mixture was left for sixteen hours at room temperature. A trace of unreacted lithium was removed by filtration and the filter washed with ether, water and then 5N hydrochloric acid. The filtrate and washings were heated on a steam bath for one hour. After cooling the reaction mixture was washed with ether and the aqueous layer was basified using aqueous sodium hydroxide solution. The reaction mixture was extracted with ether and the extract dried and the ether removed to give a residue from which N-methyl-1-(1-phenylcyclobutyl)butylamine (b.p. 80°–86°/0.1 mm Hg.) was distilled.

The amine (2.3 g) prepared as described above was dissolved in ether (40 ml) and hydrogen chloride gas passed through the solution to precipitate N-methyl-1-(1-phenylcyclobutyl)butylamine hydrochloride (mp. 196°–197° C.). (Formula I R_1=propyl; R_2=H; R_3=Me; R_4, R_5 and R_6 are H.)

EXAMPLE 26

A solution of 1-(3-chloro-5-methylphenyl)-1-cyclobutanecarbonitrile (8.0 g) in ether (40 ml) was

added to a solution of propyl magnesium bromide [prepared by the reaction of 1-bromopropane (6.7 g) and magnesium (1.3 g)] in ether (80 ml) and the mixture heated under reflux for two and a half hours. Two thirds of the ether was evaporated off and then, after cooling, a solution of sodium borohydride (3.5 g) in ethanol (150 ml) added. The mixture was maintained at 50° C. for one hour and water (50 ml) and then 5N hydrochloric acid (50 ml) added. The ether layer was separated, dried and evaporated to yield a solid which was recrystallised from propan-2-ol to give 1-[1-(3-chloro-5-methylphenyl)cyclobutyl]butylamine hydrochloride (m.p. 145°–146° C.).

The hydrochloride salt prepared as above was shaken with ether and 5N sodium hydroxide solution and the ether layer evaporated to give the primary amine which was converted into N,N-dimethyl-1-[1-(3-chloro-5-methylphenyl)cyclobutyl]butylamine hydrochloride (m.p. 148° C.) (Formula I R_1=propyl; R_2=H; R_3 and R_4=Me; R_5=3-Cl and R_6=5-Me) in a similar manner to that described in Example 2.

EXAMPLE 27

1-Acetyl-1-(3,4-dichlorophenyl)cyclobutane prepared as described in Example 1 (4.86 g) and cyclohexylamine (2.28 ml) were heated and stirred under reflux for 30 minutes. Stirring and heating was continued on an oil bath at 145° C. for 3 hours. The product was cooled to ambient temperature, dissolved in methanol (50 ml) and sodium borohydride (0.8 g) added. The mixture was stirred at ambient temperature for twenty hours and then poured into water and the resulting mixture extracted with ether. The ether extract was washed with water and dried. After removal of the solvent N-cyclohexyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine (b.p. 144°–156°/0.6 mm Hg) was obtained by distillation (Formula I R_1=Me; R_2=H; R_3=cyclohexyl; R_4=H; R_5=4-Cl; R_6=3-Cl).

EXAMPLE 28

Pharmaceutical compositions containing any one of the compounds of formula I disclosed in Examples 1 to 27 are prepared in the following manner.

EXAMPLE 28(a)

Tablets are prepared from the following ingredients:

	Parts by Weight
Active Ingredient	50.0
Lactose	78.5
Polyvinylpyrrolidone	5.0
Maize Starch	15.0
Magnesium Stearate	1.5

The active ingredient, the lactose and some of the starch are mixed and granulated with a solution of the polyvinylpyrrolidone in ethanol. The granulate is mixed with the stearic acid and the rest of the starch and the mixture is compressed in a tabletting machine to give tablets containing 50.0 mg. of the active ingredient.

EXAMPLE 28(b)

Capsules are prepared in the following way. A mixture of the active ingredient (45 parts by weight) and lactose powder (205 parts by weight) is filled into hard gelatin capsules, each capsule containing 45 mg. of the active ingredient.

EXAMPLE 28(c)

In the preparation of enteric coated tablets, the tablets described in Example 28(a) are given a thin coat of shellac varnish, followed by 20 coats of cellulose acetate phthalate in a manner well known in the art. In a similar manner the capsules of Example 28(b) may be provided with an enteric coating.

EXAMPLE 28(d)

Vials containing a solution of water-soluble compounds of the present invention suitable for injection are prepared from the following ingredients:

Active Ingredient	1100 g.
Mannitol	1100 g.
Water, freshly distilled	to 11 liters

The active ingredient and mannitol are dissolved in some of the water and the volume of the solution is adjusted to 11 liters. The resulting solution is sterilised by filtration and filled into sterile vials each containing 1.65 mL of solution.

EXAMPLE 28(e)

In the preparation of suppositories, 100 parts by weight of the finely ground active ingredient is incorporated in 1214 parts by weight of triglyceride suppository base and the mixture is formed into suppositories each containing 100 mg. of the active ingredient.

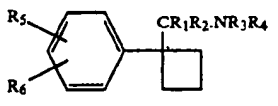
In the preceding Examples novel ketones of formula V have been disclosed in which R_1, R_5 and R_6 have the meaning given in Examples 1, 1(a) to 1(e), 3, 4, 4(a) to 4(e), 6, 7, 7(a) to 7(d) 9, 9(a) to 9(n), 10, 10(a) to 10(z), 10(aa), 10(bb), 11(i), 11(k) and 11(l). These novel ketones of formula V are prepared by hydrolysis of novel imines of formula XI in which Y=MgBr and R_1, R_5 and R_6 have the meaning given in the Examples specified above.

In the preceding Examples novel cyano compounds of formula XII are disclosed in which R_5 and R_6 have the meaning given in Examples 1, 1(d), 1(e), 4(g), 9(e), 9(m), 10(k), 10(e), 10(p), 10(r), 10(v), 10(y), 10(z), 10(aa), 10(bb), 11(k), 11(l) and 26.

In the preceding Examples novel formamides of formula XVII are disclosed in which R_1, R_3, R_5, R_6, R_7, R_8 have the meaning given in Examples 1, 1(a) to 1(e), 3, 4, 4(a) to 4(e), 6, 7, 7(a) to 7(d), 9, 9(a) to 9(n), 10, 10(a) to 10(z), 10(aa), 10(bb), 11(i), 11(k), 11(l).

We claim:

1. A compound of the formula I:



I

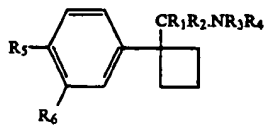
or a pharmaceutically acceptable salt thereof in which R_1 is branched chain alkyl of up to 6 carbon atoms, in which R_2 is selected from the group consisting of H and alkyl groups containing 1 to 3 carbon atoms; in which R_3 and R_4, which are the same or different, are selected from the group consisting of H, straight or branched

chain alkyl groups containing 1 to 4 carbon atoms, alkenyl groups having 3 to 6 carbon atoms, alkynyl groups having 3 to 6 carbon atoms, cycloalkyl groups in which the ring contains 3 to 7 carbon atoms, and a group of formula CHO; in which R_5 and R_6, which are the same or different, are selected from the group consisting of H, halo, trifluoromethyl, alkyl groups containing 1 to 3 carbon atoms, alkoxy groups containing 1 to 3 carbon atoms, alkythio groups containing 1 to 3 arbon atoms and phenyl, or R_5 and R_6, together with the carbon atoms to which they are attached, form a second benzene ring optionally substituted by at least one halo, alkyl or alkoxy group containing 1 to 4 carbon atoms or the substituents of the second benzene ring together with the two carbon atoms to which they are attached form a further benzene ring.

2. A compound according to claim 1 in which R_1 is branched chain alkyl of up to 4 carbon atoms, and R_2 is H or methyl.

3. A compound according to claim 2 in which R_1 is isopropyl, isobutyl or sec-butyl, R_3 and R_4 are selected from the group consisting of H, methyl, ethyl and formyl, and R_5 and R_6 are selected from the group consisting of H, fluoro, chloro, bromo, iodo, trifluoromethyl, methyl, methoxy and phenyl, or R_5 and R_6 together with the carbon atoms to which they are attached form a second benzene ring optionally substituted by halo.

4. A compound according to claim 1 of the formula III:



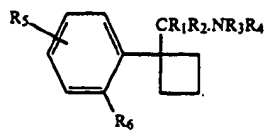
III

or a pharmaceutically acceptable salt thereof in which R_1 is branched chain alkyl of up to 6 carbon atoms; R_2 is selected from the group consisting of H and alkyl groups containing 1 to 3 carbon atoms; R_3 and R_4, which are the same or different, are selected from the group consisting of H, straight or branched chain alkyl groups containing 1 to 4 carbon atoms, alkenyl groups having 3 to 6 carbon atoms, alkynyl groups having 3 to 6 carbon atoms, cycloalkyl groups in which the ring contains 3 to 7 carbon atoms, and a group of formula CHO; R_5 and R_6, which are the same or different are selected from the group consisting of H, halo, trifluoromethyl, alkyl groups containing 1 to 3 carbon atoms, alkoxy groups containing 1 to 3 carbon atoms, alkythio groups containing 1 to 3 carbon atoms and phenyl, or R_5 and R_6, together with the carbon atoms to which they are attached, form a second benzene ring optionally substituted by at least one halo, alkyl or alkoxy group containing 1 to 4 carbon atoms or the substituents of the second benzene ring together with the two carbon atoms to which they are attached form a further benzene ring.

5. A compound according to claim 4 in which R_1 is branched chain alkyl of up to 4 carbon atoms and R_2 is H or methyl.

6. A compound according to claim 4 in which R_1 is isopropyl, isobutyl or sec-butyl, R_3 and R_4 are selected from the group consisting of H, methyl, ethyl and formyl, and R_5 and R_6 are selected from the group consisting of H, fluoro, chloro, bromo, iodo, trifluoromethyl, methyl, methoxy and phenyl, or R_5 and R_6 together with the carbon atoms to which they are attached form a second benzene ring optionally substituted by halo.

7. A compound according to claim 1 of the formula IV:

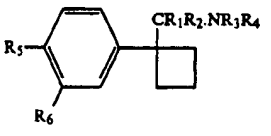


IV

or a pharmaceutically acceptable salt thereof in which R_1 is branched chain alkyl of up to 6 carbon atoms; R_2 is selected from the group consisting of H and alkyl groups containing 1 to 3 carbon atoms; R_3 and R_4, which are the same or different, are selected from the group consisting of H, straight or branched chain alkyl groups containing 1 to 4 carbon atoms, alkenyl groups having 3 to 6 carbon atoms, alkynyl groups having 3 to 6 carbon atoms, cycloalkyl groups in which the ring contains 3 to 7 carbon atoms, and a group of formula CHO; R_5 is H, halo, trifluoromethyl, alkyl groups containing 1 to 3 carbon atoms, alkoxy groups containing 1 to 3 carbon atoms, alkythio groups containing 1 to 3 carbon atoms or phenyl, and R_6 is fluoro or methyl.

8. A compound according to claim 7 in which R_1 is isopropyl, isobutyl or sec-butyl; R_2 is H or methyl; R_3 and R_4 are selected from the group consisting of H, methyl, ethyl and formyl; R_5 is H, fluoro, chloro, bromo, iodo, trifluoromethyl, methyl, methoxy or phenyl and R_6 is fluoro or methyl.

9. A compound according to claim 1 of the formula III:



III

or a pharmaceutically acceptable salt thereof in which R_1 is isobutyl; R_2 is H; R_3 is H, methyl or ethyl; R_4 is H, methyl or ethyl; R_5 is chloro; and R_6 is H or chloro.

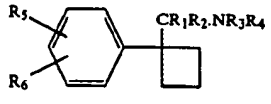
10. A compound of claim 9 which is N-methyl-1-[1-(4-chlorophenylcyclobutyl]-3-methyl-butylamine or a pharmaceutically acceptable salt thereof.

11. A compound of claim 9 which is N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine or a pharmaceutically acceptable salt thereof.

12. A compound of claim 9 which is N,N-dimethyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]-3-methylbutylamine or a pharmaceutically acceptable salt thereof.

13. A compound of claim 9 which is α-[1-(4-chlorophenyl)cyclobutyl]benzylamine or a pharmaceutically acceptable salt thereof.

14. A pharmaceutical composition useful for treating depression in humans which comprises an anti-depressantly effective amount of a compound of the formula I:



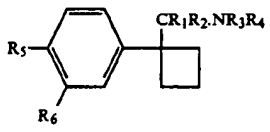
I

or a pharmaceutically acceptable salt thereof in which R_1 is branched chain alkyl of up to 6 carbon atoms,; R_2 is selected from the group consisting of H and alkyl groups containing 1 to 3 carbon atoms; R_3 and R_4, which are the same or different, are selected from the group consisting of H, straight or branched chain alkyl groups containing 1 to 4 carbon atoms, alkenyl groups having 3 to 6 carbon atoms, alkynyl groups having 3 to 6 carbon atoms, cycloalkyl groups in which the ring contains 3 to 7 carbon atoms, and a group of formula CHO; R_5 and R_6, which are the same or different are selected from the group consisting of H, halo, trifluoromethyl, alkyl groups containing 1 to 3 carbon atoms, alkoxy groups containing 1 to 3 carbon atoms, alkythio groups containing 1 to 3 carbon atoms and phenyl, or R_5 and R_6, together with the carbon atoms to which they are attached, form a second benzene ring optionally substituted by at least one halo, alkyl or alkoxy group containing 1 to 4 carbon atoms or the substituents of the second benzene ring together with the two carbon atoms to which they are attached form a further benzene ring.

15. A composition according to claim 14 in which R_1 is branched chain alkyl of up to 4 carbon atoms, and R_2 is H or methyl.

16. A composition according to claim 15 in which R_1 is isopropyl, isobutyl or sec-butyl, R_3 and R_4 are selected from the group consisting of H, methyl, ethyl and formyl, and R_5 and R_6 are selected from the group consisting of H, fluoro, chloro, bromo, iodo, trifluoromethyl, methyl, methoxy and phenyl, or R_5 and R_6 together with the carbon atoms to which they are attached form a second benzene ring optionally substituted by halo.

17. A composition according to claim 14 wherein the compound is of the formula III:



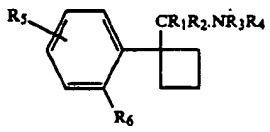
III

or a pharmaceutically acceptable salt thereof in which R_1 is branched chain alkyl of up to 6 carbon atoms,; R_2 is selected from the group consisting of H and alkyl groups containing 1 to 3 carbon atoms; R_3 and R_4, which are the same or different, are selected from the group consisting of H, straight or branched chain alkyl groups containing 1 to 4 carbon atoms, alkenyl groups having 3 to 6 carbon atoms, alkynyl groups having 3 to 6 carbon atoms, cycloalkyl groups in which the ring contains 3 to 7 carbon atoms, and a group of formula CHO; R_5 and R_6, which are the same or different are selected from the group consisting of H, halo, trifluoromethyl, alkyl groups containing 1 to 3 carbon atoms, alkoxy groups containing 1 to 3 carbon atoms, alkythio groups containing 1 to 3 carbon atoms and phenyl, or R_5 and R_6, together with the carbon atoms to which they are attached, form a second benzene ring optionally substituted by at least one halo, alkyl or alkoxy group containing 1 to 4 carbon atoms or the substituents of the second benzene ring together with the two carbon atoms to which they are attached form a further benzene ring.

18. A composition according to claim 17 in which R_1 is branched chain alkyl of up to 4 carbon atoms, and R_2 is H or methyl.

19. A composition according to claim 17 in which R_1 is isopropyl, isobutyl or sec-butyl, R_3 and R_4 are selected from the group consisting of H, methyl, ethyl and formyl, and R_5 and R_6 are selected from the group consisting of H, fluoro, chloro, bromo, iodo, trifluoromethyl, methyl, methoxy and phenyl, or R_5 and R_6 together with the carbon atoms to which they are attached form a second benzene ring optionally substituted by halo.

20. A composition according to claim 14 of the formula IV:

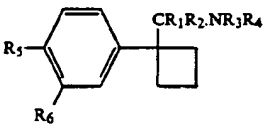


IV

or a pharmaceutically acceptable salt thereof in which R_1 is branched chain alkyl of up to 6 carbon atoms; R_2 is selected from the group consisting of H and alkyl groups containing 1 to 3 carbon atoms; R_3 and R_4, which are the same or different, are selected from the group consisting of H, straight or branched chain alkyl groups containing 1 to 4 carbon atoms, alkenyl groups having 3 to 6 carbon atoms, alknynyl groups having 3 to 6 carbon atoms, cycloalkyl groups in which the ring contains 3 to 7 carbon atoms, and a group of formula CHO; R_5 is H, halo, trifluoromethyl, alkyl groups containing 1 to 3 carbon atoms, alkoxy groups containing 1 to 3 carbon atoms, alkythio groups containing 1 to 3 carbon atoms or phenyl, and R_6 is fluoro or methyl.

21. A composition according to claim 14 in which R_1 is isopropyl, isobutyl or sec-butyl,; R_2 is H or methyl, R_3 and R_4 are selected from the group consisting of H, methyl, ethyl and formyl,, R_5 is H, fluoro, chloro, bromo, iodo, trifluoromethyl, methyl, methoxy or phenyl and R_6 is fluoro or methyl.

22. A composition according to claim 14 wherein the compound is of the formula III:



III

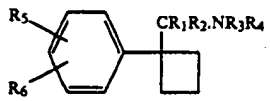
or a pharmaceutically acceptable salt thereof in which R_1 is isobutyl; R_2 is H; R_3 is H, methyl or ethyl; R_4 is H, methyl or ethyl; R_5 is chloro; and R_6 is H or chloro.

23. A composition according to claim 22 wherein the compound is N-methyl-1-[1-(4-chlorophenylcyclobutyl]-3-methylbutylamine or a pharmaceutically acceptable salt thereof.

24. A composition according to claim 22 wherein the compound is N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine or a pharmaceutically acceptable salt thereof.

25. A composition according to claim 22 wherein the compound is N,N-dimethyl-1-[1-(3,4-dichlorophenyl)-cyclobutyl]-3-methylbutylamine or a pharmaceutically acceptable salt thereof.

26. A method of treating depression in humans which comprises administering to a human in need thereof an anti-depressantly effective amount of a compound of the formula I:



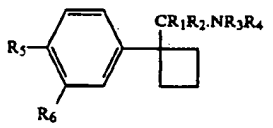
I

or a pharmaceutically acceptable salt thereof in which R_1 is branched chain alkyl of up to 6 carbon atoms,; R_2 is selected from the group consisting of H and alkyl groups containing 1 to 3 carbon atoms; R_3 and R_4, which are the same or different are selected from the group consisting of H, straight or branched chain alkyl groups containing 1 to 4 carbon atoms, alkenyl groups having 3 to 6 carbon atoms, alkynyl groups having 3 to 6 carbon atoms, cycloalkyl groups in which the ring contains 3 to 7 carbon atoms, and a group of formula CHO; R_5 and R_6, which are the same or different, are selected from the group consisting of H, halo, trifluoromethyl, alkyl groups containing 1 to 3 carbon atoms, alkoxy groups containing 1 to 3 carbon atoms, alkythio groups containing 1 to 3 carbon atoms and phenyl, or R_5 and R_6, together with the carbon atoms to which they are attached, form a second benzene ring optionally substituted by at least one halo, alkyl or alkoxy group containing 1 to 4 carbon atoms or the substituents of the second benzene ring together with the two carbon atoms to which they are attached form a further benzene ring, in combination with a pharmaceutically acceptable carrier.

27. A method according to claim 26 in which R_1 is branched chain alkyl of up to 4 carbon atoms, and R_2 is H or methyl.

28. A method according to claim 27 in which R_1 is isopropyl, isobutyl or sec-butyl, R_3 and R_4 are selected from the group consisting of H, methyl, ethyl and formyl, and R_5 and R_6 are selected from the group consisting of H, fluoro, chloro, bromo, iodo, trifluoromethyl, methyl, methoxy and phenyl or R_5 and R_6 together with the carbon atoms to which they are attached form a second benzene ring optionally substituted by halo.

29. A method according to claim 26 wherein the compound is of the formula III:



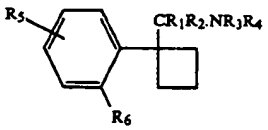
III

or a pharmaceutically acceptable salt thereof in which R_1 is branched chain alkyl of up to 6 carbon atoms; R_2 is selected from the group consisting of H and alkyl groups containing 1 to 3 carbon atoms; R_3 and R_4, which are the same or different, are selected from the group consisting of H, straight or branched chain alkyl groups containing 1 to 4 carbon atoms, alkenyl groups having 3 to 6 carbon atoms, alkynyl groups having 3 to 6 carbon atoms, cycloalkyl groups in which the ring contains 3 to 7 carbon atoms, and a group of formula CHO; R_5 and R_6, which are the same or different, are selected from the group consisting of H, halo, trifluoromethyl, alkyl groups containing 1 to 3 carbon atoms, alkoxy groups containing 1 to 3 carbon atoms, alkythio groups containing 1 to 3 carbon atoms and phenyl, or R_5 and R_6, together with the carbon atoms to which they are attached, form a second benzene ring optionally substituted by at least one halo, alkyl or alkoxy group containing 1 to 4 carbon atoms or the substituents of the second benzene ring together with the two carbon atoms to which they are attached form a further benzene ring.

30. A method according to claim 29 in which R_1 is branched chain alkyl of up to 4 carbon atoms and R_2 is H or methyl.

31. A method according to claim 29 in which R_1 is isopropyl, isobutyl or sec-butyl, R_3 and R_4 are selected from the group consisting of H, methyl, ethyl and formyl, and R_5 and R_6 are selected from the group consisting of H, fluoro, chloro, bromo, iodo, trifluoromethyl, methyl, methoxy and phenyl, or R_5 and R_6 together with the carbon atoms to which they are attached form a second benzene ring optionally substituted by halo.

32. A method according to claim 29 of the formula IV:

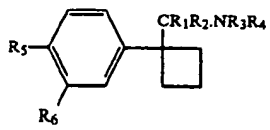


IV

or a pharmaceutically acceptable salt thereof in which R_1 is branched chain alkyl of up to 6 carbon atoms,; R_2 is selected from the group consisting of H and alkyl groups containing 1 to 3 carbon atoms; R_3 and R_4, which are the same or different are selected from the group consisting of H, straight or branched chain alkyl groups containing 1 to 4 carbon atoms, alkenyl groups having 3 to 6 carbon atoms, alkynyl groups having 3 to 6 carbon atoms, cycloalkyl groups in which the ring contains 3 to 7 carbon atoms, and a group of formula CHO; R_5 and R_6, which are the same or different are selected from the group consisting of H, halo, trifluoromethyl, alkyl groups containing 1 to 3 carbon atoms, alkoxy groups containing 1 to 3 carbon atoms, alkylthio groups containing 1 to 3 carbon atoms and phenyl, or R_5 and R_6, together with the carbon atoms to which they are attached, form a second benzene ring optionally substituted by at least one halo, alkyl or alkoxy group containing 1 to 4 carbon atoms or the substituents of the second benzene ring together with the two carbon atoms to which they are attached form a further benzene ring and R_6 is fluoro or methyl.

33. A method according to claim 32 in which R_1 is isopropyl, isobutyl or sec-butyl, R_2 is H or methyl, R_3 and R_4 are selected from the group consisting of H, methyl, ethyl and formyl, R_5 is H, fluoro, chloro, bromo, iodo, trifluoromethyl, methyl, methoxy or phenyl and R_6 is fluoro or methyl.

34. A method according to claim 29 wherein the compound is of the formula III:



III

or a pharmaceutically acceptable salt thereof in which R_1 is isobutyl; R_2 is H; R_3 is H, methyl or ethyl; R_4 is H, methyl or ethyl; R_5 is chloro; and R_6 is H or chloro.

* * * * *

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

JAMES E. JEFFERY ET AL

Serial No.:	725,206	Art Unit:	124
Filed :	April 19, 1985	Examiner:	P. Shaver
For :	THERAPEUTIC AGENTS		

TERMINAL DISCLAIMER

Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

Applicants, JAMES E. JEFFERY, ANTONIN KOZLIK and ERIC C. WILMSHURST, subjects and residents of Great Britain, hereby waive and disclaim the terminal portion of the term of the patent to be granted upon the above identified Application subsequent to June 11, 2002, the date of expiration of their issued United States Patent No. 4,522,828, whereby the patent to be granted on this application and U.S. Patent No. 4,522,828 will expire on the same day, provided that the patent to be granted on the above application shall expire immediately if it ceases to be commonly owned with said Patent No. 4,522,828.

Respectfully submitted,

Date: 6 March 1987 — James E. Jeffery
JAMES. E. JEFFERY

Date: 6. March 1987 — Antonin Kozlik
ANTONIN KOZLIK

Date: July 18, 1986 — Eric C. Wilmshurst
ERIC C. WILMSHURST

CONSENT OF ASSIGNEE

THE BOOTS COMPANY, P.L.C., a British corporation located at Pennyfoot Street, Nottingham NG2 3AA, England, the owner of the entire right, title and interest in the above application Serial No. 725,202 and said U.S. Patent No. 4,522,828, hereby consents and agrees to the aforesaid Terminal Disclaimer executed by James E. Jeffery, Antonin Kozlik and Eric C. Wilmshurst.

THE BOOTS COMPANY, P.L.C.

By: _____
Authorized Signatore

Date: _____

APPROVED FOR SIGNATURE MCJ
M. A. THACKER

Patent Maintenance Fees - Public Inquiry

Patent#: 4746680 Filed: 04/19/85 Issued: 05/24/88 Serial#: 06725206
Status: 12th Year Fee Window Opens: 05/24/99 Sml Entity: NO
Window Opens: 05/24/99 Surchg Due: 11/24/99 Expiration: 05/24/00
Fee Amt Due:$ 3160 Surchg Amt Due:$ Total Amt Due:$ 3160
Fee Code: 185 Surchg Code:
Title: THERAPEUTIC AGENTS

Address For Fee Purposes:
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901 N. WASHINGTON STREET
SUITE 305
ALEXANDRIA VA 22314

Most Recent Significant Events:

09/26/95	Payment of Maintenance Fee, 8th Year, Large Entity
08/02/93	Payor Number Assigned
09/30/91	Payment of Maintenance Fee, 4th Year, PL 97-247
	Last Event On Maintenance History

Attachment
E

Chronology of Significant Activities

Regarding the MERIDIA™ IND and NDA

IND 27-624	
December 20, 1985	Original IND submission (IND 27-624)
December 24, 1985	Date of receipt of the IND by the FDA
January 14, 1986	CMC amendment, clinical amendment
January 24, 1986	Effective date of the IND
February 28, 1986	Clinical amendment
March 17, 1986	General comments on the IND from the FDA (Company response sent on February 18 and 24, 1988)
May 27, 1986	Clinical amendment
June 20, 1986	Clinical amendment
July 1, 1986	CMC amendment
September 18, 1986	Clinical amendment
January 9, 1987	Clinical amendment
March 11, 1987	Clinical amendment, pharmacology/toxicology amendment
April 1, 1987	IND annual report
September 21, 1987	DMF amendment
September 29, 1987	Clinical amendment
November 13, 1987	Clinical amendment
February 18, 1988	Response to FDA's letter dated March 11, 1986 (pre-clinical and clinical)
February 24, 1988	Response to FDA's letter dated March 11, 1986 (CMC)
March 1, 1988	Clinical amendment, pharmacology/toxicology amendment
March 3, 1988	IND annual report
April 20, 1988	Clinical amendment

October 28, 1988	Clinical amendment
January 18, 1989	CMC amendment
March 9, 1989	Pharmacology/toxicology amendment
March 13, 1989	IND annual report
March 30, 1989	Pharmacology/toxicology amendment
September 25, 1989	Clinical amendment
September 27, 1989	Clinical amendment, CMC amendment
November 2, 1989	Clinical amendment
December 1, 1989	Clinical amendment
December 13, 1989	Clinical amendment
January 9, 1990	Clinical amendment
February 5, 1990	Clinical amendment
February 26, 1990	Clinical amendment
March 12, 1990	IND annual report
March 29, 1990	Clinical amendment
April 2, 1990	Information amendment - company name change
May 10, 1990	Clinical amendment
July 11, 1990	Clinical amendment
July 23, 1990	Clinical amendment
August 8, 1990	Clinical amendment
September 7, 1990	Clinical amendment
November 2, 1990	Clinical amendment
January 29, 1991	Clinical amendment
March 14, 1991	Clinical amendment
April 9, 1991	Clinical amendment
May 1, 1991	Clinical amendment
June 14, 1991	IND annual report
July 15, 1991	Clinical amendment
August 20, 1991	Clinical amendment
August 27, 1991	CMC amendment

February 19, 1992	Clinical amendment
March 17, 1992	IND annual report
April 29, 1992	Clinical amendment
May 29, 1992	Pharmacology/toxicology amendment
June 25, 1992	Clinical amendment
July 23, 1992	Meeting with FDA to discuss Phase II study plan
August 10, 1992	CMC amendment
August 28, 1992	Request to include women of child bearing potential (permission granted by the FDA on October 13, 1992)
November 5, 1992	Clinical amendment
November 15, 1992	Clinical amendment
December 23, 1992	Clinical amendment
December 23, 1992	Clinical amendment
December 23, 1992	Clinical amendment
March 17, 1993	Pharmacology/toxicology amendment
March 19, 1993	IND annual report
March 30, 1993	Clinical amendment
April 19, 1993	CMC amendment
May 21, 1993	Clinical amendment
June 23, 1993	Transfer of IND to Endocrine and Metabolism Division
June 24, 1993	CMC inquiry
October 20, 1993	Clinical amendment
November 2, 1993	Clinical amendment
December 14, 1993	End of Phase II meeting with the FDA
December 14, 1993	Clinical amendment
February 16, 1994	Clinical amendment
March 3, 1994	CANDA - planning meeting with the FDA
March 17, 1994	IND annual report
April 6, 1994	Clinical amendment
April 22, 1994	Clinical amendment
April 28, 1994	Clinical amendment

May 31, 1994	FDA's written comments on clinical studies presented at the meeting on December 14, 1993
June 3, 1994	Clinical amendment
June 27, 1994	Demonstration of the CANDA prototype project
June 30, 1994	Meeting with the HFD-170, FDA
July 7, 1994	Clinical amendment
August 2, 1994	Clinical amendment
August 24, 1994	Clinical amendment
September 20, 1994	Clinical amendment
November 8, 1994	Clinical amendment
November 11, 1994	CMC amendment
November 23, 1994	Clinical amendment
December 2, 1994	CMC amendment
January 5, 1995	Clinical amendment
March 15, 1995	IND annual report
March 22, 1995	Clinical amendment
March 24, 1995	Clinical amendment
May 3, 1995	Clinical amendment
May 4, 1995	Pre-NDA meeting with the FDA
June 1, 1995	Response to FDA's comments at the pre-NDA meeting
June 15, 1995	CANDA meeting with FDA, DISD Group
July 7, 1995	CMC queries/proposal
July 10, 1995	CANDA demonstration meeting with the FDA
September 25, 1995	CMC amendment
September 27, 1995	Clinical amendment
October 27, 1995	Clinical amendment
December 18, 1995	Clinical amendment
December 21, 1995	Clinical amendment
March 1, 1996	Clinical amendment
April 19, 1996	Clinical amendment
April 19, 1996	Clinical amendment
April 25, 1996	Clinical amendment

June 3, 1996	IND annual report
June 20, 1996	Clinical amendment
June 26, 1996	Clinical amendment
July 29, 1996	Clinical amendment
July 31, 1996	Clinical amendment
August 26, 1996	Clinical amendment
September 19, 1996	Clinical amendment
September 23, 1996	Clinical amendment
September 24, 1996	Clinical amendment
October 23, 1996	Clinical amendment
October 30, 1996	Clinical amendment
November 15, 1996	Clinical amendment
January 6, 1997	Clinical amendment
April 14, 1997	IND annual report
April 24, 1997	Protocol amendment
July 1, 1997	Protocol amendment
NDA 20-632	
August 7, 1995	Original NDA submission
August 7, 1995	Field copies of required sections of the NDA submitted to the New Orleans District Office
August 9, 1995	Date of receipt of the NDA by the FDA
August 21, 1995	CANDA - report section submission
August 28, 1995	Corrections to the environmental assessment
September 19, 1995	Revised electronic files of oncogenicity data
October 25, 1995	Investigator information, protocol and CRFs to Office of Scientific Investigations.
October 27, 1995	NDA filing letter received from the FDA
November 14, 1995	CANDA - clinical data base submission
November 28 - December 4, 1995	Pre-approval inspection of the Shreveport plant
December 1, 1996	Response to queries from CMC reviewer (telephone call November 21, 1995)

December 6, 1995	Response to Biopharmaceutics questions raised in the October 27, 1996 filing letter and submission of electronic files of efficacy data requested by the biometrics reviewer on October 24, 1995.
December 8, 1995	Additional electronic files of efficacy data requested by the FDA on December 7, 1995
December 13, 1995	Submission of 12 month stability report on qualification lots
December 19, 1995	Four-month (120 day) safety update
December 20, 1995	Electronic files of additional efficacy data submitted
February 5, 1996	FDA request for additional analysis of clinical studies
February 8, 1996	Teleconference with FDA clinical and statistical staff

February 9, 1996	Methods validation package updated to reflect list of samples collected during pre-approval inspection and answers to CMC reviewer's questions
February 13, 1996	Additional information to FDA office of scientific investigations
February 15, 1996	Electronic files of summary of pharmacokinetic data (response to February 9, 1996 request)
February 27, 1996	Request from HFD-170 for a full package of information on abuse potential
March 5, 1996	Response to reviewer questions (February 5, 1996) on clinical studies
March 13, 1996	Submission of abuse liability information (clinical)
March 15, 1996	Request for additional analyses of clinical studies
March 19, 1996	Proposal to add 20 mg capsules
March 20, 1996	Abuse liability (pre-clinical) submission
April 23, 1996	Meeting with the FDA
April 2, 1996	Request for additional analyses from clinical studies
April 3, 1996	Electronic files of summaries of pharmacokinetic reports to Biopharmaceutics reviewer
April 8, 1996	Background material submitted for April 23, 1996 meeting
April 9, 1996	Response to questions on clinical studies
April 22, 1996	Partial response to questions on various studies (April 2, 1996)
May 2, 1996	Electronic files clinical data in response to a request from Biometrics reviewer on April 26, 1996)
May 10, 1996	CMC amendment to add 20 mg strength
May 13, 1996	Phase IIIb study protocols to the FDA
May 15, 1996	Final response to clinical queries on April 2, 1996
June 5, 1996	Reviewer comments on abuse potential (Company response submitted on August 8, 1996)
June 20, 1996	Clinical response
June 13, 1996	FDA extended the NDA review period by 3-months
June 25, 1996	Environmental assessment reviewers comments/requests
July 15, 1996	Meeting with the FDA
July 18, 1996	Electronic files of clinical data (requested by the FDA July 16, 1996)

August 1, 1996	GLP/QA statements - response to Pharmacology/Toxicology reviewer's question
August 6, 1996	FDA comments on abuse potential protocols
August 8, 1996	Partial response to FDA comments on abuse potential (June 5, 1996)
August 12, 1996	Clarification of issues raised at the July 25, 1996 meeting
August 23, 1996	Abuse potential response to reviewer comments June 5, 1996
August 27, 1996	Response to Environmental Assessment reviewer's comments of June 25, 1996
August 30, 1996	Background package to the FDA Advisory Committee Office
September 13, 1996	Cardio-Renal Division review received from the FDA
September 18, 1996	Phase IV proposals to the FDA
September 20, 1996	Submission of additional analyses to the FDA
September 23, 1996	Pharmacology/toxicology amendment
October 4, 1996	Protocols of placebo controlled obesity studies to HFD-170
October 4, 1996	Second safety update
September 26, 1996	FDA Endocrine and Metabolism Advisory Committee Meeting to discuss MERIDIA
October 4, 1996	Submission of copies of slides presented at the Advisory Committee Meeting on September 26, 1996
October 8, 1996	Meeting with the FDA
October 9, 1996	Additional analyses of clinical data submitted to the FDA
October 14, 1996	Submission of additional analyses of clinical data
October 15, 1996	Submission of information requested by the CMC reviewer
October 16, 1996	Additional analyses of clinical data submitted to the FDA
October 17, 1996	Submission of additional analyses of clinical data
October 17, 1996	Comments on clinical abuse potential studies received - FDA's response to August 23, 1996 submission
October 21, 1996	Meeting with Endocrine and Metabolism Division
October 25, 1996	Revised draft package insert with 20 mg strength added
October 28, 1996	Meeting with HFD-170 to discuss abuse potential
October 29, 1996	Request for additional pre-clinical studies from HFD-170
October 29, 1996	Submission of DMF to the NDA (as requested by CMC reviewer)
November 8, 1996	FDA approvable letter received

November 12, 1996	Intention to file an amendment
November 18, 1996	Request for meeting with HFD-170
December 17, 1996	Background information for meeting with HFD-170 on January 9, 1997 - abuse potential
January 3, 1997	Partial response to approvable letter
January 9, 1997	Meeting with the FDA to discuss abuse potential
January 14, 1997	Pre-clinical information - response to the pharmacology/toxicology reviewer
January 17, 1997	Request from the FDA for additional data analysis (submitted January 23, 1997)
January 23, 1997	Response to FDA request for additional data
January 29, 1997	Revised PI
February 5, 1997	Electronic files of the revised PI
February 10, 1997	ISS update
February 14, 1997	PPI submission
February 18, 1997	FDA comments/requests from the meeting on January 9, 1997
February 27, 1997	Submission of pre-clinical reports and request for a meeting with HFD-170 and HFD-510 to discuss abuse potential
March 11, 1997	FDA minutes of the January 9, 1997 and October 28, 1996 meetings
April 2, 1997	Results of abuse potential studies and request for a meeting with HFD-170
April 15, 1997	Submission of the minutes of the January 9, 1997 and October 28, 1996 meetings
May 23, 1997	Response to approvable letter, results of one abuse potential study
May 29, 1997	Facsimile from the FDA request for clarification of data sets
June 2, 1997	FDA acknowledgement of major amendment dated May 23, 1997
June 4, 1997	Response to FDA facsimile of May 29, 1997
June 5, 1997	Electronic copy of the package insert and patient package insert
June 13, 1997	Response to FDA question in May 21, 1997 meeting regarding possible differences in the lots used in human drug abuse studies
June 17, 1997	Submission of overheads presented at drug abuse meeting on May 21, 1997.
July 2, 1997	Request for meeting with HFD-170

September 4, 1997	Response to FDA question on May 21, 1997 provides dissolution profiles for the lots used in human drug abuse studies
September 16, 1997	Facsimile from the FDA recommending language for the drug abuse and dependence section of the physician label.
September 19, 1997	Submission of the proposed labeling for the drug abuse and dependence section of the package insert
September 29, 1997	Follow-up to September 25, 1997 teleconference relating to the methodology and equipment used to collect echocardiographic data
October 8, 1997	Response to telephone request regarding the qualifications of echocardiographers
October 10, 1997	Facsimile from the FDA providing revisions to the package insert.
October 20, 1997	Third safety update
October 21, 1997	Submission of the protocol for the collection of echocardiographic data and the statistical analysis plan
October 28, 1997	Response to FDA facsimile dated October 10, 1997 providing revisions to the package insert
October 30, 1997	Submission of the summary of valve function from echocardiographic data
November 7, 1997	Submission of echocardiographic screening report
November 13, 1997	Revised patient package insert based on teleconference of November 5, 1997 and telefax November 6, 1997
November 19, 1997	Response to teleconference on November 18, 1997 providing additional revisions to the patient package
November 21, 1997	Facsimile from the FDA recommending changes in the physician labeling and patient labeling
November 21, 1997	Submission of draft bottle labels
November 22, 1997	Response to FDA facsimile dated November 21, 1997 requesting revisions to the package insert and patient package insert
November 22, 1997	Phase IV commitment
November 22, 1997	FDA letter of approval for MERIDIA

PATENT
Attorney Docket No.: 01289.0002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	U.S. Patent 4,746,680
Issued:	May 24, 1988
To:	James E. Jeffery, Antonin Kozlik, and Eric C. Wilmshurst
Assignee:	Knoll AG
Title of Patent:	THERAPEUTIC AGENTS

Assistant Commissioner for Patents
Box Patent EXT.
Washington, D.C. 20231

Sir:

CERTIFICATION

I, CHARLES E. VAN HORN, do hereby certify that this accompanying application for extension of the term of U.S. Patent 4,746,680 under 35 U.S.C. § 156 including its attachments and supporting papers is being submitted as one original and four (4) copies thereof.

Respectfully submitted,

Charles E. Van Horn

Charles E. Van Horn
Reg. No. 40,266

Dated: January 20, 1998

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202-408-4000

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Assistant Commissioner for Patents
Box Patent EXT.
Washington, D.C. 20231

Sir:

DECLARATION ACCOMPANYING APPLICATION
UNDER 35 U.S.C. § 156 FOR EXTENSION OF PATENT TERM

I, CHARLES E. VAN HORN, do hereby declare:

I am a patent attorney authorized to practice before the United States Patent and Trademark Office and I have been appointed as attorney by the Patent Assignee, Knoll Aktiengesellschaft, with regard to this application for extension of the term of U.S. Patent 4,746,680 and to transact all business in the U.S. Patent and Trademark Office in connection therewith.

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I have reviewed and understand the contents of the accompanying application being submitted pursuant to 37 C.F.R. § 1.740.

I believe that the patent is subject to extension pursuant to § 1.710.

I believe that an extension of the length claimed is justified under 35 U.S.C. § 156 and applicable regulations.

I believe the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in § 1.720.

Respectfully submitted,

Charles E. Van Horn

Charles E. Van Horn
Reg. No. 40,266

Dated: January 20, 1998

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